AUGMENTATION OF BRAIN FUNCTION: FACTS, FICTION AND CONTROVERSY

VOLUME III: FROM CLINICAL APPLICATIONS TO ETHICAL ISSUES AND FUTURISTIC IDEAS

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VOLUME III: FROM CLINICAL APPLICATIONS TO ETHICAL ISSUES AND FUTURISTIC IDEAS

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The final volume in this tripartite series on Brain Augmentation is entitled "From Clinical Applications to Ethical Issues and Futuristic Ideas". Many of the articles within this volume deal with translational efforts taking the results of experiments on laboratory animals and applying them to humans. In many cases, these interventions are intended to help people with disabilities in such a way so as to either restore or extend brain function.

Traditionally, therapies in brain augmentation have included electrical and pharmacological techniques. In contrast, some of the techniques discussed in this volume add specificity by targeting select neural populations. This approach opens the door to *where* and *how* to promote the best interventions. Along the way, results have empowered the medical profession by expanding their understanding of brain function. Articles in this volume relate novel clinical solutions for a host of neurological and psychiatric conditions such as stroke, Parkinson's disease, Huntington's disease, epilepsy, dementia, Alzheimer's disease, autism spectrum disorders (ASD), traumatic brain injury, and disorders of consciousness.

In disease, symptoms and signs denote a departure from normal function. Brain augmentation has now been used to target both the core symptoms that provide specificity in the diagnosis of a disease, as well as other constitutional symptoms that may greatly handicap the individual. The volume provides a report on the use of repetitive transcranial magnetic stimulation (rTMS) in ASD with reported improvements of core deficits (i.e., executive functions). TMS in this regard departs from the present-day trend towards symptomatic treatment that leaves unaltered the root cause of the condition. In diseases, such as schizophrenia, brain augmentation approaches hold promise to avoid lengthy pharmacological interventions that are usually riddled with side effects or those with limiting returns as in the case of Parkinson's disease. Brain stimulation can also be used to treat auditory verbal hallucination, visuospatial (hemispatial) neglect, and pain in patients suffering from multiple sclerosis.

The brain acts as a telecommunication transceiver wherein different bandwidth of frequencies (brainwave oscillations) transmit information. Their baseline levels correlate with certain behavioral states. The proper integration of brain oscillations provides for the phenomenon of binding and central coherence. Brain augmentation may foster the normalization of brain oscillations in nervous system disorders. These techniques hold the promise of being applied remotely (under the supervision of medical personnel), thus overcoming the obstacle of travel in order to obtain healthcare.

At present, traditional thinking would argue the possibility of synergism among different modalities of brain augmentation as a way of increasing their overall effectiveness and improving therapeutic selectivity. Thinking outside of the box would also provide for the implementation of brain-to-brain interfaces where techniques, proper to artificial intelligence, could allow us to surpass the limits of natural selection or enable communications between several individual brains sharing memories, or even a global brain capable of self-organization.

Not all brains are created equal. Brain stimulation studies suggest large individual variability in response that may affect overall recovery/treatment, or modify desired effects of a given intervention. The subject's age, gender, hormonal levels may affect an individual's cortical excitability. In addition, this volume discusses the role of social interactions in the operations of augmenting technologies. Finally, augmenting methods could be applied to modulate consciousness, even though its neural mechanisms are poorly understood.

Finally, this volume should be taken as a debate on social, moral and ethical issues on neurotechnologies. Brain enhancement may transform the individual into someone or something else. These techniques bypass the usual routes of accommodation to environmental exigencies that exalted our personal fortitude: learning, exercising, and diet. This will allow humans to preselect desired characteristics and realize consequent rewards without having to overcome adversity through more laborious means. The concern is that humans may be playing God, and the possibility of an expanding gap in social equity where brain enhancements may be selectively available to the wealthier individuals. These issues are discussed by a number of articles in this volume. Also discussed are the relationship between the diminishment and enhancement following the application of brain-augmenting technologies, the problem of "mind control" with BMI technologies, free will the duty to use cognitive enhancers in high-responsibility professions, determining the population of people in need of brain enhancement, informed public policy, cognitive biases, and the hype caused by the development of brain-augmenting approaches.

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Table of Contents

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What do temporal lobe epilepsy and progressive mild cognitive impairment have in common?

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Temporal lobe epilepsy (TLE) and mild cognitive impairment (MCI) are both subject to intensive memory research. Memory problems are a core characteristic of both conditions and we wonder if there are analogies which would enrich the two distinct research communities. In this review we focus on memory decline in both conditions, that is, the most feared psychosocial effect. While it is clear that memory decline in MCI is highly likely and would lead to the more severe diagnosis of Alzheimer's disease, it is a debate if TLE is a dementing disease or not. As such, like for MCI, one can differentiate progressive from stable TLE subtypes, mainly depending on the age of onset. Neuroimaging techniques such as volumetric analysis of the hippocampus, entorhinal, and perirhinal cortex show evidence of pathological changes in TLE and are predictive for memory decline in MCI. Several studies emphasize that it is necessary to extend the region of interest—even whole-brain characteristics can be predictive for conversion from MCI to Alzheimer's disease. Electroencephalography is increasingly subject to computational neuroscience, revealing new approaches for analyzing frequency, spatial synchronization, and information content of the signals. These methods together with event-related designs that assess memory functions are highly promising for understanding the mechanisms of memory decline in both TLE and MCI populations. Finally, there is evidence that the potential of such markers for memory decline is far from being exhausted. Similar structural and neurophysiological characteristics are linked to memory decline in TLE and MCI. We raise the hope that interdisciplinary research and cross-talk between fields such as research on epilepsy and dementia, will shed further light on the dementing characteristics of the pathological basis of MCI and TLE and support the development of new memory enhancing treatment strategies.

Keywords: epilepsy, mild cognitive impairment, subjective cognitive complaints, memory decline, neuroimaging, neurophysiology

1. INTRODUCTION

Memory problems are a core symptom of amnestic mild cognitive impairment (MCI) (Stewart, 2012a), but are also one of the chief complaints of patients with temporal lobe epilepsy (TLE) (Helmstädter, 2002; Butler and Zeman, 2008). Even worse, quality of life is negatively influenced by memory impairment (Fisher et al., 2000). This superficial analogy is not only a possible link between TLE and MCI but can serve as starting point from which researchers in each field may add innovative aspects to their respective research areas. Detection of early prognostic markers of memory deficits in MCI and TLE would obviously pave the way for new therapeutic programs, for memory augmentation, and treatment of memory deficits, possibly reducing the overall prevalence of memory disorders and improving quality of life in these patients (DeKosky and Marek, 2003; Geda, 2012).

Current research endeavors are focused on early diagnosis of MCI and TLE. In the case of MCI it is clear that neuropsychological tests alone are not sufficient, since they are not sensitive enough for patients with subjective complaints and no significant and clinically detectable deficits (Stewart, 2012b). Analogously, electroencephalographic assessment and imaging may lead to dubious findings, or no findings at all, in the epileptogenesis or latency period of epilepsy (Engel et al., 2013). Because of the various aetiologies and pathologic processes that may lead to memory impairment, it is suggested that a combination of several biomarkers is necessary to provide an early diagnosis with reliable prognostic validity (DeKosky and Marek, 2003). In this review, we want to highlight promising biomarkers from a pool of structural and electroencephalographical measures for which prognostic validity was evidenced for one of the two clinical groups with similar cognitive impairments, TLE and MCI. While prediction of memory decline and conversion to Alzheimer's disease is an established field of research, prognosis of memory decline in TLE mainly focuses on the prediction of post-surgical memory impairment and only rarely on the prediction of change over the course of the disorder; in this review, we focus on the latter case. As such, we identify commonalities between the two disorders, which could give rise to new approaches in research.

2. NEUROPSYCHOLOGY AND PROGNOSIS

TLE is most often associated with impaired long-term memory (Hermann et al., 1997). In addition to problematic long-term

memory, MCI is especially annoying for patients because of impairment of prospective memory (van den Berg et al., 2012). Patients with epilepsy rank cognitive dysfunction highest among the problems experienced (Fisher et al., 2000). However, in many cases such impairments are not detected by standard neuropsychological tests of memory functions, so that complaints about memory decline commonly mismatch with test performance (Butler and Zeman, 2008). Specifically, standard test intervals ranging from some hours to days are too short to detect impaired long-term memory. Indeed, it is the episodic memory which is affected in TLE (Helmstädter, 2002). In addition, it seems difficult to tell from neuropsychological tests alone if patients are already impaired during encoding or if they just fail to retrieve learned information. Similarly, it is necessary to distinguish free recall of memories from recognition. Thus, research should take into consideration the existence of inter-individual differences with respect to the type of impairment, i.e., encoding or retrieval, recall or recognition, within the specific pathologies.

Epileptic seizures might trigger neurodegenerative changes leading eventually to memory impairments (Helmstädter, 2002; Stefan and Pauli, 2008). However, the question whether TLE is a dementing disease due to seizure activity is under debate (Helmstaedter and Elger, 1999, 2009; Jokeit and Ebner, 1999, 2002; Dodrill, 2004; Elger et al., 2004; Mantoan et al., 2009; Gonzalez et al., 2012). The typical course of epilepsy includes in the early phase a long silent period after the brain insult before recurrent seizures start, which then allows an accurate diagnosis (see Najm et al., 2001, for a review on epidemiology and risk factors). The early evolution is often caused by a structural lesion, that is, the epileptogenic lesion (Rosenow and Lüders, 2001). In fact, memory deficits correlate well with the age of the early precipitating event. This might produce an artificial correlation of memory impairment with the duration of epilepsy (Kaaden and Helmstaedter, 2009). For example, no difference between the extent of memory deficits at the time of the first diagnosis and a 5-year follow up was found (Äikiä et al., 2001), suggesting a non-progressive course of memory deficits in TLE. In fact, Helmstaedter and co-workers found that memory decline which is specific to TLE occurs in childhood and early adolescence, while a further progress of loss of memory functions runs in parallel with normal aging (Helmstaedter and Elger, 2009). On the other hand, deficits are more severe in patients with chronic TLE as compared with newly diagnosed patients (Äikiä et al., 2001). Similarly, there is a correlation between time and severity of memory impairments for patients with long chronic course (>27 years) but only for those with more than 10 secondarily generalized seizures per year, and not for complex-partial seizures (Stefan and Pauli, 2002). There are further studies suggesting that patients with a longer duration of refractory TLE exhibit more severe cognitive impairments (Hattiangady and Shetty, 2008; Stefan and Pauli, 2008; Mantoan et al., 2009). However, a longitudinal study over at least 10 years at the stage of severe, chronic and intractable epilepsy showed that duration has less influence on cognitive decline than what was found in cross-sectional studies (Thompson and Duncan, 2005). Most importantly, in this study it was demonstrated that in refractory epilepsy a high frequency of tonic-clonic seizures was the strongest predictor for cognitive decline. However, it is necessary to disentangle the influence of the underlying causes, such as mitochondrial dysfunction or inflammatory causes from seizure activity (Helmstaedter, 2007). It is obvious that progressive brain diseases, such as a malignant brain tumor, lead to a progressive pathology of memory function and it is therefore important to provide an accurate diagnosis which allows identification of progressive comorbidity.

Epileptic seizures can occur also at the stage of MCI or early Alzheimer's disease (Vossel et al., 2013) and the initial diagnosis of late-onset TLE, more specifically the epileptic amnesic syndrome, can be indicative for development of MCI and Alzheimer's disease (Cretin et al., 2012). Most interestingly, Vossel and co-workers reported that cognitive decline is detectable in patients with amnestic MCI or Alzheimer's disease on average 6.8 (MCI) or 5.5 (Alzheimer's disease) years earlier in the case of comorbid epilepsy (Vossel et al., 2013). It is important to note that epileptic symptoms predated memory symptoms or at least showed up contemporaneously.

Finally, memory deficits in TLE may be caused by clinical or subclinical seizure activity, structural, or other underlying brain pathology, adverse effects of anticonvulsant medication, and psychological mechanisms (Butler and Zeman, 2008; Hermann et al., 2010). Helmstaedter suggests that assessing two types of patients could explain contributory mechanisms of memory decline (Helmstädter, 2002). The first type includes newly diagnosed TLE patients at first presentation, i.e., after experiencing first seizures. The second type includes TLE patients with chronic course and drug resistant seizures. A follow-up measurement of memory performance should help to answer the question whether memory deficits are progressive or not. However, examining newly diagnosed TLE patients is a challenge. After the first or second seizure, a patient is usually not subjected to cost-intensive, extensive examinations, such as long-term video-monitoring which is the gold standard to reliably establish a diagnosis. Instead, in clinical practice an appropriate first line medication is chosen in order to control seizures, even if the type of epilepsy is not fully elucidated. Again, simple and reliable biomarkers to ascertain diagnosis at this early stage are highly warranted. For example, in a large multicenter study, hippocampal T2 hyperintensity and impaired hippocampal growth were found to be an early biomarker for epilepsy after febrile status epilepticus in children (Lewis et al., 2013).

A similar challenge is met by family doctors with respect to MCI. The first examination in primary care needs to reliably distinguish between age-associated memory impairment (Hänninen and Soininen, 1997), subjective memory complaints, and MCI (Stewart, 2012a,b). Classification is performed according to the global deterioration scale for aging and dementia (Reisberg et al., 1982). This scale stages individuals into Level 1, being free of both subjective and objective clinical deficits, Level 2, having subjective deficits only, Level 3, having subtle deficits in cognition and some impairments in executive functioning, affecting complex occupational and social activities, and finally Level 4, having clear deficits in cognition and functioning with reduced performance in instrumental activities of daily life (Gauthier et al., 2006). Thus, patients which present memory complaints in primary care without fulfilling the criteria for MCI are considered to suffer from

so-called subjective memory complaints. These complaints are not related to significant deficits on neuropsychological scales but could still be an early form of a neurodegenerative disorder since this diagnosis implies high risk to experience further decline toward MCI (Reisberg et al., 2010). It contrast, it is possible that a patient who is diagnosed as suffering from subjective cognitive complaints has simply detected an age-associated memory impairment, which can be a symptom of normal aging. As such, subjective complaints do not necessarily correlate with progress of decline (Förstl et al., 1995). However, the diagnosis of age-associated memory impairment does not imply that the patient's memory performance is normal (Goldman and Morris, 2001). A normal test-performance can still be seen after a significant decline when the patient's starting level of memory was high. As such, neuropsychological tests cannot identify progressive memory decline alone.

If a patient has ascertained the diagnosis of MCI, the diagnosis can be further refined into amnestic, multi-domain and single, non-memory-domain subtypes (Winblad et al., 2004), as well as into a stable and a progressive group. While 30–50% of newly diagnosed MCI patients do not experience further decline of cognitive functions over 3–5 years, or even return to normal, the residual 50–70% show progress toward a more severe form of impairment (Rossini et al., 2007). This broad range of progression rates results from a large number of studies, in which inclusion and exclusion criteria varied to some degree. It is possible that correlating neuropsychological progression to specific biomarkers could yield less variable estimations of conversion rates. Therefore, the following sections of this review are dedicated to promising biomarkers in the fields of neuroimaging and neurophysiology. Finally, we close with an outlook on possible strategies for augmentation of memory function with respect to the discussed biomarkers.

3. NEUROIMAGING

Neuroimaging is of high value for diagnosis and prognosis of neurodegenerative diseases (Borghesani et al., 2010) such as MCI (Winblad et al., 2004). A characteristic symptom in MCI is atrophy of the medial temporal lobe, including memory related structures such as the hippocampus. Brain atrophy correlates with the progression of cognitive decline at the stage of subjective cognitive complaints (Förstl et al., 1995). More specifically, medial temporal lobe atrophy is able to predict progression to dementia in patients with MCI (Korf et al., 2004) with a reasonable predictive value (positive and negative predictive values 0.44 and 0.91, respectively Geroldi et al., 2006).

Decreased volumes of hippocampal formations are also a common finding in TLE patients. There is a relation between degree of memory impairment and seizure frequency, but it is suggested that structural pathologies in the temporal lobe rather than seizures cause memory difficulties (Butler and Zeman, 2008). However, these pathologies may be the consequence as well as the cause of seizures (Mathern et al., 2002a) and there are controversial findings in these respects. While neuronal cell loss in the hippocampus is not related to duration of the epilepsy, decreased neuronal density in the dentate gyrus evidenced by histology correlates positively with memory impairment in patients with TLE (Pauli et al., 2006). In addition, TLE is also associated with reduced neurogenesis in this region, further contributing to the decreased neuronal density (Mathern et al., 2002b). Neurogenesis of functional granule cells in the dentate gyrus of the hippocampus might facilitate hippocampal-dependent learning and episodic memory (Hattiangady and Shetty, 2008; Kuruba et al., 2009). On the other hand, some studies have indicated a correlation between epilepsy duration and neuronal loss (Mathern et al., 1995, 2002a). In other words, reduced neurogenesis and/or neuronal loss in this region in the chronic stage of TLE may be closely related to impairments in learning, memory, and other cognitive functions. In fact, it seems that the origin of memory problems in TLE is in childhood or adolescence (Helmstaedter and Elger, 2009). Well in line with this, hippocampal sclerosis is associated with poorer performance independent of age. However, temporal lobe atrophy is not present in all TLE patients. (Bernasconi et al., 2000) averaged six slices containing the head, body, and tail of the hippocampus. They found that the obtained hippocampal T2 relaxation times better predicted the epileptic focus than analyzing atrophy. Most interestingly, in addition to hippocampal damage, entorhinal lesions seem to play a special role in memory impairment in TLE. Especially lesions in layer III which are frequently found in TLE (Schwarcz and Witter, 2002). These findings and the importance of the rhinal cortex for memory consolidation (Axmacher et al., 2008) suggest that extracting biomarkers of the rhinal cortex may shed further light on memory problems in TLE. Thus, it is very likely that also other characteristics and other regions need to be addressed in the debate of whether memory decline in TLE is progressive or not.

Since hippocampal volumes discriminate patients with Alzheimer's disease and correlate with episodic memory performance, the volume and shape of this structure has the potential for a valid biomarker (Mueller et al., 2012). However, the hippocampus is not the only relevant structure in memory deficits. Research in MCI and Alzheimer's disease suggests that it is possibly not even the most relevant one. Volumetry of the hippocampal formation with Magnetic Resonance Imaging (MRI) revealed a relative risk of 0.69 for transition from MCI to Alzheimer's disease (Jack et al., 1999). A recent review suggests that perirhinal lesions have a stronger impact on memory functions than hippocampal lesions (Salig, 2009). Thus, atrophy of both structures, hippocampus and entorhinal cortex, may be a better marker for MCI, than either one of these alone (Winblad et al., 2004). Similarly, for TLE patients, entorhinal and perirhinal cortices are reduced in volume. Atrophy of the entorhinal cortex ipsilateral to the seizure onset zone is only found in patients with TLE, but not in other forms of epilepsy (Bernasconi et al., 2003). In addition, there is evidence that a global cortical atrophy marker such as widening of cerebrospinal fluid spaces might also be predictive for conversion from MCI to Alzheimer's disease (Teipel et al., 2007). Well in line with this, in MCI and Alzheimer's disease brain atrophy is prominent in the medial temporal lobe but also widespread over posterior cingulate and neocortical temporoparietal regions (Fox et al., 2001). Similarly, gray-matter decrease in the hippocampal area, inferior and middle temporal gyrus, posterior cingulate, and precuneus is greater in patients who convert from MCI to Alzheimer's disease than

in non-converters (Chételat et al., 2005). Moreover, entorhinal and perirhinal cortices reveal reduced numbers of cells before the hippocampus is affected by degeneration (Dickerson and Sperling, 2008). The special role of the enthorinal cortex is further supported by a study which revealed that best classification accuracy of MCI was based on enthorinal cortex volume and best classification accuracy of Alzheimer's disease was based on hippocampal volume (Pennanen et al., 2004). Similarly, enthorinal cortex thickness was found to predict further memory decline in established Alzheimer's disease (Velayudhan et al., 2013). Thus, it would be worth analyzing more globally defined markers for atrophy or different combinations of regions, depending on the questions being asked.

However, by interpreting the role of hippocampal volumetry for predicting memory decline we have to consider the large variation between protocols for the delineation of the hippocampus in MR images. Up to date, there is no consistently applied standard which would allow comparing results of different studies to each other. Major differences refer to inclusion and exclusion of hippocampal white matter, definition of the anterior hippocampal—amygdala border, definition of the posterior border, and the extent to which the hippocampal tail is included, definition of the inferior medial border of the hippocampus, and use of varying arbitrary lines (Konrad et al., 2008). Therefore, it is difficult to estimate the real validity of volumetry in predicting memory decline. Alternatively, hippocampal shape features may be used instead of hippocampal volumetry. (Gerardin et al., 2009) utilized these shape features to train a support vector machine in order to perform multidimensional classification. The resulting classification rates were 94% for patients with Alzheimer's disease and 83% for MCI patients. Regarding the entorhinal cortex, reliable findings support stability of cortical thickness, volume, and surface area in normal aging (Lemaitre et al., 2012). The average cortical thickness over a region is a feature which is mostly independent from defined borders. Finally, to account for global atrophy, measures of intensity and deformation were of high predictive value for memory decline (Duchesne et al., 2010). Similarly, whole brain atrophy measures are predictive for conversion from MCI to Alzheimer's disease (Jack et al., 2005; Spulber et al., 2010).

Another promising MR technique is Diffusion Tensor Imaging (DTI). The potential of DTI for diagnosing MCI and its ability to predict further decline might have been underestimated so far, possibly due to a higher variability of fractional anisotropy than volumetric measures (Mueller et al., 2012). Indeed, DTI has been shown to be superior to hippocampal volumetry in distinguishing MCI from healthy controls (Muller et al., 2007). Hippocampal diffusivity predicts conversion from amnestic MCI to Alzheimer's disease at least as well as hippocampal atrophy (Kantarci et al., 2005; Fellgiebel et al., 2006).

4. NEUROPHYSIOLOGY

Clinical EEG is the standard neurophysiological test in patients with epilepsy, with a high positive and low negative predictive value of epileptiform discharges, such as spikes and sharp waves in routine recordings. While the literature on EEG-biomarker for localization of the seizure-onset zone is overwhelming, the information about memory-relevant biomarkers is scarce, and there is even less literature about prediction of memory decline.

Analysis of peak-frequency showed that poorer memory performance coincides with lower alpha peak (Ripper et al., 2001). Similarly, in children with epilepsy the differential activation of memory-resources has been documented with event-related power changes in the theta and lower-alpha range (Krause et al., 2008). Thus, assessing frequency properties of the EEG in TLE patients may reveal memory-relevant features. As such, using the rat pilocarpine model of TLE, it was found that spatial memory declines soon after status epilepticus and that these deficits correlate with a decrease of theta power but not with interictal-like activity in the hippocampus (Chauviere et al., 2009). Similarly to results from cross-sectional studies in humans (Helmstaedter and Elger, 2009), the loss of spatial memory ability is stable and not progressive in this model.

Intracranial EEG is only used in presurgical assessment to better delineate the seizure onset zone (Foldvary-Schaefer, 2004) and cannot be applied in the early stages of TLE. Indeed, neurophysiological parameters have been underutilized to assess the functional deficit zone, including memory deficits in patients with TLE (Grunwald and Vannucci, 2004). Event related designs, assessing brain signals in response to items that have to be memorized and recalled, are well suited to identify abnormal patterns in the surface and intracranial EEG of patients. We suggest that it would be of interest if such designs could help identifying abnormal changes over time in patients with TLE.

Despite the fact that the use of EEG for diagnosis of Alzheimer's disease or MCI is not a standard in clinical practice, a large number of studies succeeded in identifying markers that distinguish patients with Alzheimer's disease from MCI. EEG-biomarkers also successfully differentiated MCI from healthy subjects (see Rossini et al., 2007, for a review). Dauwels et al. (2010) summarize characteristics of the EEG in these clinical groups. First, the EEG is dominated by slower frequencies (Bonanni et al., 2008). Fast Fourier Transformations (FFTs) show a relative increase of activity below 8 Hz and decrease above this range. This characteristic was the first measure used in quantitative EEG-evaluation in MCI patients (Prichep et al., 1994) and therefore probably the most well known in the field. However, this slowing is possibly caused by perturbations in synchronization and decreased neural complexity (Cantero et al., 2009), representing two characteristic features of EEG in MCI. Synchrony can be expressed as Pearson's correlation coefficient, coherence, Granger causality, information-theoretic and state space based synchrony measures, phase synchrony indices, stochastic event synchrony, spatial distribution of phase synchrony, and small world network characteristics, among others (see Dauwels et al., 2010, for a review). Different measures of synchronization may be increased or decreased in MCI depending on frequency range, type of analysis, and regions being assessed (Jelic et al., 2000; Stam et al., 2003; Pijnenburg et al., 2004; Koenig et al., 2005; Babiloni et al., 2006). In addition, analysis of complexity of EEG signals is a valuable approach for resting EEG (Stam, 2005). Therefore, we suggest to apply complexity analysis for prognostic assessments. For example one could use approximate entropy, auto mutual information, sample entropy, multiscale entropy, Lempel-Ziv

complexity, Hjorth parameters, Petrosian fractal dimension, or Higuchi fractal dimension (see also Bao et al., 2009; Dauwels et al., 2010).

It is remarkable that assessing frequency characteristics of MCI patients differentiates progressive from stable patients. It was found that a reduction of alpha power over posterior leads is characteristic for the progressive subgroup (Luckhaus et al., 2008). Despite this success, it is acknowledged that markers of resting EEG largely overlap between progressive MCI and stable MCI (Giannakopoulos et al., 2009). For example, it was shown that measures based on frequency analysis are valuable approaches for diagnosis and they change over the course of progression, but have no prognostic validity at baseline (Jelic et al., 2000). Thus, such markers (i.e., theta and beta power) have to be recorded longitudinally to detect changes which correlate with cognitive decline. It is suggested to use event-related EEG dynamic analysis to examine neocortical circuits and neuronal networks in order to predict memory decline (Giannakopoulos et al., 2009). The major advantage of doing memory research using event related designs in the EEG is the high temporal resolution, showing immediately pathologically delayed responses. In fact, it was found that delayed components of the event-related potential differ between stable and progressive MCI (Missonier et al., 2007). As such, it is highly likely that the combination of frequency, complexity, and synchrony characteristics in event-related EEG can shed further light on the progressive nature of MCI and eventually also of memory characteristics in TLE.

Since both TLE and MCI have impaired long-term memory, it is reasonable compare the mechanisms of successful and non-successful memory formation. A large number of studies have aimed at identifying the markers in the event related potential. The studies looked at efficient encoding which was recorded during the patient's learning of items. This was compared to the patient's recall performance in a later session (Fernández et al., 2002; Voss and Paller, 2007). Another approach refers to the dual route theory of recognition, that is, familiarity and recollection components (see Rugg and Curran, 2007, for a review). Familiarity is impaired in Alzheimer's disease but to some extent preserved in amnestic MCI while recollection is impaired in both clinical groups (Ally et al., 2009). However, other research groups report that familiarity is preserved in Alzheimer's disease and MCI for pictures (Westerberg et al., 2006), and that familiarity is impaired to at least the same extent as recollection in amnestic MCI, distinguishing MCI from normal aging population but not from Alzheimer's disease (Wolk et al., 2008). These findings from functional research are well in line with decreased volume of the perirhinal cortex and the hippocampus. While the perirhinal cortex mediates familiarity, the hippocampus is considered a core region for recollection (Turriziani et al., 2008; Brown et al., 2010). Thus, when designing event-related EEG studies the dimensions of familiarity and recollection, as well as encoding and retrieval, have to be addressed.

5. AUGMENTATION OF MEMORY FUNCTION

There are several strategies to augment human memory, and some of these are candidates for future treatment strategies in the here discussed patient populations. Madan (2014) discusses nootropic agents, brain stimulation, mnemonic strategies, and external aids as possible approaches to support memory. These strategies include common ones such as caffeine and notes, but also implanted devices which stimulate deep brain structures electrically. The hippocampus is an obvious target for memory stimulation. For example, it was found that working memory in rats could be transferred from one animal to the other by applying hippocampal firing patterns via electrical stimulation (Deadwyler et al., 2013). Deep brain stimulation in the entorhinal cortex of epilepsy patients enhanced spatial memory (Suthana et al., 2012). Similarly, in-phase stimulation during long-term encoding in the rhinal cortex and the hippocampus of epileptic patients modulated memory performance (Fell et al., 2013) and stimulation in the fornix of Alzheimer's patients activated entorhinal and hippocampal regions, which lead to improved memory (Laxton et al., 2010). Thus, it is not surprising that Alzheimer's disease and temporal lobe epilepsy were mentioned as possible target for deep brain stimulation and memory enhancement (Suthana and Fried, 2014).

However, these stimulation techniques are still at an experimental stage and can't be used in every single patient. Specifically, most stimulation studies were performed in epilepsy patients with intracranial electrodes implanted for pre-surgical evaluation. In contrast, cognitive intervention is an established strategy for memory augmentation in MCI (Rapp et al., 2002; Simon et al., 2012). The changes are not only measurable by the assessment of memory function, but also with fMRI (Simon et al., 2012), and can be enhanced by incorporating emotional content into the training (Broster et al., 2012). While there have been several endeavors to support the validity of cognitive training in MCI or dementia, there is still room for research in temporal lobe epilepsy.

6. CONCLUSIONS

Even if the debate of whether TLE is a dementing disease or if there are just a few subtypes with progressive course is still ongoing, there is a lot of literature about structural markers for impaired memory whereas the literature about EEG-markers is scarce. Valid biomarkers, which can reliably predict conversion from MCI to Alzheimer's disease, could shed new light on the question of whether TLE is a disorder with progressive memory decline. It is likely that memory decline occurs in TLE patients with early onset but after a certain age does not result in a progressive course. There may be elderly patients with MCI-like symptoms who instead suffer from late-onset epilepsy and could be misdiagnosed. The biomarkers summarized in this review could help determine the mechanisms of memory loss at early-onset of TLE and, most importantly, identify patients with late-onset TLE.

Prediction of conversion from MCI to Alzheimer's disease has been paid much attention so far, but TLE research and specifically intracranial recordings in presurgical evaluations may help to find new biomarkers for both disorders. For example, the importance of the rhinal cortex for memory consolidation has been shown by use of intracranial EEG in TLE research and can be translated into prediction of memory loss in MCI by use of structural imaging. As such, functional EEG is a promising approach which should be paid more attention in the future, since it allows one

to combine the strength of neuropsychological assessments and the physiological assessment of brain function at a high temporal resolution.

Finally, the mentioned structures could be target for stimulating interventions such as deep brain stimulation in the rhinal, entorhinal, and hippocampal regions. The basis for these stimulation studies are the knowledge about the functional relevance of the mentioned structures but also about the involved EEG-oscillations. While deep brain stimulation is at an experimental stage we should not forget about the good effects of cognitive intervention, being established in MCI and having the potential of enhancing memory function in TLE patients.

AUTHOR CONTRIBUTIONS

Conception, decision on which references to include, revising, and approving of this work was carried out by all authors. The first author wrote the manuscript in accordance with the intellectual input of all authors. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Augmentation of cognitive function in epilepsy

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Epilepsy is one of the most common neurological disorders in humans afflicting more than 1% of the population and 65 million people worldwide (England et al., 2012). The most common form of acquired epilepsy is temporal lobe epilepsy (TLE), and over 30% of patients with TLE have seizures that are refractory to commonly used anticonvulsant drugs (Bauer and Burr, 2001). Mesial temporal lobe sclerosis (MTS) is the most common pathological abnormality in TLE (Bronen et al., 1997). The histopathological hallmarks of hippocampal sclerosis include segmental loss of pyramidal neurons, granule cell dispersion, and reactive gliosis (Sutula et al., 1989). Indeed, changes in the integrity of hippocampus and surrounding hippocampal white matter is postulated to influence overall temporal lobe network connectivity, hippocampus efficiency, seizures (Cadotte et al., 2009), and memory function (Eichenbaum et al., 2007, 2012). Indeed, animal and human studies show that abnormalities in the hippocampus and its white matter inputs and outputs are correlated with the severity of memory dysfunction (Christidi et al., 2011).

TEMPORAL LOBE CONNECTIVITY IN TLE: FILLING GAPS IN KNOWLEDGE

Patterned inputs to the hippocampus from mediobasal cortical regions and entrorhinal cortex are hypothesized to support critical memory functions of recollection (controlled, deliberate recall) and familiarity (automatic, item-based memory), respectively (Eichenbaum and Lipton, 2008; Eichenbaum et al., 2012; Dixon et al., 2014). An integrated theory of parahippocampal (PHc), perirhinal (PRc), entrorhinal (ERc), and hippocampal (HC) functioning [the 'Binding of Items and Context [BIC] Model (Diana et al., 2007)], suggests that these structures form an integrated circuit that supports recollection and familiarity. The PRc is proposed to be important in encoding and retrieving items (e.g., objects, words, and ideas), whereas the PHc is responsible for representing spatial, temporal, and semantic context. The HC supports memory for episodes by integrating these inputs and binding the item-based contextual information together as a unique event in space and time. In this view, the formation of new memories depends upon the integrated series of inputs from PRc and PHc components of the parahippocampal gyrus and their respective targets in the ERc and hippocampus. Despite extensive animal work, it is unknown in humans whether selective damage to these areas or their interconnections that produce subtypes of memory impairment might differentially respond to different types of memory training. Although some data exists on the efficacy of memory rehabilitation programs, little is known about the neural basis of individualized rehabilitation responses from a mechanistic perspective (Wagner, 2011).

IMPLICATIONS FOR MEMORY REHABILITATION

Understanding individual differences in morphological and connectional components of medial temporal lobe injury in TLE can lead to identification of subtypes of memory impairment, and thus help identify clinically important targets for memory augmentation. Our hypothesis is that the subtypes of memory impairment that result will preferentially respond to specific memory interventions, a notion that is also being addressed in the aphasia treatment literature (Kim et al., 2011). To this end, an emerging method for treating neurologically-induced memory impairment is non-invasive brain stimulation (NIBS), including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). Both tDCS and TMS are safe for use in human subjects (Nitsche et al., 2003b), and have been used widely to test hypothesis about causal links between specific brain structures supporting cognition and memory (Dayan et al., 2013; Hummel, 2014). Indeed, several studies support the use of NIBS techniques as tools for enhancing cognitive function in normal subjects and as therapeutic agents for individuals with psychiatric and neurologic disorders (Hummel and Cohen, 2006; Miniussi et al., 2008). NIBS consist of applying a weak (0.5–2.0 mA in tDCS) direct current through the scalp and skull. Depending on the polarity of the current during stimulation, NIBS may increase or decrease the rate of neuronal firing by modulating the resting membrane potentials (Creutzfeldt et al., 1962; Bindman et al., 1964; Liebetanz et al., 2002; Nitsche et al., 2003a; Zaghi et al., 2010). Although these studies are preliminary, they do provide reassuring proof-of-principle that the stimulated brain region is part of a critical circuit for performing the task under investigation.

The application of brain stimulation in combination with specific memory

rehabilitation methods (Stringer and Small, 2011) has been put forth as a strategy to compensate for basic defects in TLE-related memory processing (Miatton et al., 2011; Sankar et al., 2012; Suthana et al., 2012; Fell et al., 2013; Hariz et al., 2013; Hartikainen et al., 2014; Suthana and Fried, 2014). These studies demonstrate that electrical neuromodulation of specific deep structures within the medial temporal lobe may have persistent benefits in memory function.

NIBS has been shown to significantly decrease seizures in individuals with treatment-resistant epilepsy (Fregni et al., 2006; Nitsche and Paulus, 2009; San-Juan et al., 2011; Varga et al., 2011; Yook et al., 2011; Auvichayapat et al., 2013; Parazzini et al., 2014). Whether NIBS techniques can also improve memory function in TLE is an area of much interest. To this end, recent reports suggest that NIBS may augment cognition in a wide array of neurologic and psychiatric disorders, including schizophrenia (Minzenberg and Carter, 2012), Alzheimer's disease (Boggio et al., 2006), depression (Brunoni et al., 2012), and post-stroke recovery (Floel, 2014). Although the underlying mechanism that produces the cognitive deficits associated with epilepsy may differ from those that produce similar deficits in other disorders, the mechanism that enables tDCS' therapeutic effect appears to transcend individual disease. These results strongly suggest that tDCS may represent an excellent potential new treatment modality for epilepsy. Therefore, future studies on the possible effects of tDCS in TLE are highly warranted. There are however, a number of significant issues that must be addressed for tDCS to become practical as a treatment for TLE.

FUTURE DIRECTIONS

While NIBS has been shown to be relatively safe, currently there is surprisingly little known about the specific mechanisms underlying the therapeutic effects (Reato et al., 2013). Nevertheless, various postulates have been put forward such as N-methyl-D-aspartate receptor mediated long and short-term potentiation modulation (Liebetanz et al., 2002; Nitsche et al., 2004; Thickbroom and Mastaglia, 2009). Studies aimed at defining the dose for NIBS techniques in space and in time, as well as determining the safe stimulation intensity parameters and electrode positions, are now critical to propel this field forward. Finally, with regard to tDCS, it was initially believed to primarily affect cortical regions directly beneath the electrode. However, there are now a number of reports based on results from computer modeling suggesting that the current during tDCS may in fact reach deeper areas, such as the hippocampus (Sadleir et al., 2010; Parazzini et al., 2012). In order to systemically reach the hippocampus and surrounding structures at therapeutic levels, computer modeling will be needed and will likely play an increasingly important role in the design of electrode montages that can consistently reach these areas in the future. Fortunately, a number of groups now use computer modeling to gain a better understanding of where current is flowing during NIBS as well as methods to guide or focus current (Datta et al., 2009; Bai et al., 2013; Dmochowski et al., 2013; Edwards et al., 2013). While NIBS techniques offer the capability to modulate large or diverse areas of the brain, it is still an open question as to what extent electrical neuromodulation in one brain area may affect adjacent or more distant areas and mechanism of action. However, recent efforts are beginning to explore these many complex issues directly (Keeser et al., 2011; Polania et al., 2011; Lamy et al., 2012; Polania et al., 2012; Park et al., 2013; Hampstead et al., 2014; Notturno et al., 2014).

Future advancements in current methodologies for NIBS may provide substantial improvements during focal delivery of stimulation to the temporal lobe for memory augmentation. Also, improvements in multi-modal non-invasive techniques such as fMRI or MEG, may be able to detect neural signatures reflective of NIBS related neurophysiological changes within the hippocampus and surrounding structures that result in memory enhancement. Through the combined use of NIBS and multiunit local field potential recordings in combination with non-invasive measurements such as EEG and fMRI studies we may be able to optimize detection and determine the precise neuronal correlates of NIBS related behavioral changes. Other training techniques such as neurofeedback may also allow patients the ability to modulate electrical stimulation oscillatory activity in order to achieve improvements in memory.

In summary, it will become increasingly important for future studies to build upon and elucidate the mechanism of action used in NIBS enhancement of memory. The location, parameters, and phase of delivery of NIBS may need to vary amongst individuals. Hence, systematic comparisons and consistent methodologies across studies will likely contribute to a solid understanding of NIBS and its effects on learning and memory. Resolution of these issues may be crucial as to whether NIBS based therapeutics will advance toward a useful treatment for patients with TLE related memory problems.

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Augmented brain function by coordinated reset stimulation with slowly varying sequences

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Several brain disorders are characterized by abnormally strong neuronal synchrony. Coordinated Reset (CR) stimulation was developed to selectively counteract abnormal neuronal synchrony by desynchronization. For this, phase resetting stimuli are delivered to different subpopulations in a timely coordinated way. In neural networks with spike timing-dependent plasticity CR stimulation may eventually lead to an anti-kindling, i.e., an unlearning of abnormal synaptic connectivity and abnormal synchrony. The spatiotemporal sequence by which all stimulation sites are stimulated exactly once is called the stimulation site sequence, or briefly sequence. So far, in simulations, pre-clinical and clinical applications CR was applied either with fixed sequences or rapidly varying sequences (RVS). In this computational study we show that appropriate repetition of the sequence with occasional random switching to the next sequence may significantly improve the anti-kindling effect of CR. To this end, a sequence is applied many times before randomly switching to the next sequence. This new method is called SVS CR stimulation, i.e., CR with slowly varying sequences. In a neuronal network with strong short-range excitatory and weak long-range inhibitory dynamic couplings SVS CR stimulation turns out to be superior to CR stimulation with fixed sequences or RVS.

Keywords: coordinated reset, slowly varying sequences, desynchronization, spike timing-dependent plasticity, anti-kindling

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Introduction

Abnormally strong neuronal synchronization characterizes several brain disorders, e.g., Parkinson's disease (Lenz et al., 1994; Nini et al., 1995; Hammond et al., 2007), epilepsy (Wong et al., 1986; Schomer and Lopes da Silva, 2010), and tinnitus (Ochi and Eggermont, 1997; Llinas et al., 1999; Weisz et al., 2005; Eggermont and Tass, 2015). Coordinated reset (CR) stimulation (Tass, 2003a,b) was developed in order to specifically counteract abnormal neuronal synchrony by desynchronization (Tass, 1999). CR stimulation means to deliver phase resetting stimuli at different times to different sub-populations involved in abnormal neuronal synchronization (Tass, 2003a,b). Computational studies showed that in neuronal populations with spike timing-dependent plasticity (STDP) (Gerstner et al., 1996; Markram et al., 1997; Bi and Poo, 1998; Feldman, 2000) CR stimulation has long-lasting, sustained effects (Tass and Majtanik, 2006; Hauptmann and Tass, 2007; Popovych and Tass, 2012). This is because

CR stimulation employs the multistability of neuronal networks with STDP (Tass and Majtanik, 2006; Hauptmann and Tass, 2007; Maistrenko et al., 2007; Popovych and Tass, 2012). CR-stimulation causes a desynchronization and in turn, due to STDP (Gerstner et al., 1996; Markram et al., 1997; Bi and Poo, 1998; Feldman, 2000), leads to a decrease of the mean synaptic weight. In this way, CR stimulation shifts the neuronal network from a pathological attractor with up-regulated synchrony and connectivity to a physiological attractor with down-regulated synchrony and connectivity (Tass and Majtanik, 2006; Hauptmann and Tass, 2007; Popovych and Tass, 2012). In this way CR applied induces an unlearning of the abnormal synaptic connectivity and abnormal neuronal synchrony, so that an anti-kindling is achieved (Tass and Majtanik, 2006).

Computational studies showed that anti-kindling can robustly be achieved in networks of spiking or bursting model neurons where the neurons interact via plastic excitatory and inhibitory synapses (Popovych and Tass, 2012; Tass and Popovych, 2012). These studies show also that anti-kindling occurs irrespective of whether CR stimulation is delivered to the somata or to excitatory or inhibitory synapses.

In accordance with these computational findings, long-lasting CR-induced desynchronization was achieved in pre-clinical as well as clinical studies with invasive and non-invasive stimulation modalities. Electrical CR stimulation induced long-lasting desynchronization in rat hippocampal slice rendered epileptic by magnesium withdrawal (Tass et al., 2009). Therapeutic long-lasting after-effects of electrical CR deep brain stimulation were observed in parkinsonian non-human primates (Tass et al., 2012b). Unilateral CR stimulation applied to the subthalamic nucleus (STN) of parkinsonian MPTP monkeys for only 2 h per day during 5 subsequent days caused significant sustained bilateral therapeutic after-effects for at least 30 days, while no after-effects were induced by standard permanent high-frequency deep brain stimulation (Tass et al., 2012b). By the same token, lasting after-effects of electrical CR stimulation of the STN were also verified in parkinsonian patients (Adamchic et al., 2014a). So far, non-invasive CR stimulation was realized with acoustic stimuli and applied to the treatment of chronic subjective tinnitus (Tass and Popovych, 2012; Tass et al., 2012a). In a proof of concept-study it was shown that acoustic CR stimulation causes a statistically and clinically significant and sustained reduction of tinnitus symptoms (Adamchic et al., 2012a,b; Tass et al., 2012a) along with a concomitant reduction of abnormal neuronal synchrony (Tass et al., 2012a; Adamchic et al., 2014b), abnormal effective connectivity (Silchenko et al., 2013) and abnormal cross-frequency coupling (Adamchic et al., 2014c) within a tinnitus-related network of brain areas.

We here set out to further improve the efficacy of CR stimulation by focusing on a key element of CR, the stimulation site sequence, i.e., the temporal sequence of activating the different stimulation sites exactly once, which in what follows will briefly be called *sequence*. Keeping the sequence constant for all stimulation cycles is optimal in neuronal networks without STDP, since it enables optimal desynchronization at minimal intensities (Tass, 2003a,b). The situation gets more sophisticated in the presence of STDP. In a network of phase oscillators with couplings subject to STDP the sequence was randomly varied from cycle to cycle in order to avoid reverberations which might possibly lead to the formation of sequence-related neuronal subclusters and/or to a delayed anti-kindling (Tass and Majtanik, 2006). However, in several computational studies addressing different aspects of CR a robust anti-kindling was achieved with CR stimulation with fixed sequence (Hauptmann and Tass, 2007, 2009; Tass and Hauptmann, 2007, 2009) as well as with sequences randomly varying form cycle to cycle (Tass and Majtanik, 2006; Tass and Hauptmann, 2006; Popovych and Tass, 2012; Tass and Popovych, 2012; Ebert et al., 2014). We denote CR stimulation with sequences randomly varied from cycle to cycle as *RVS CR stimulation*, i.e., CR with rapidly varying sequences, whereas CR stimulation with fixed sequence is called *FS CR stimulation*, i.e., CR stimulation with fixed sequence. Although some findings indicated that RVS CR might lead to a quicker anti-kindling (Tass and Majtanik, 2006), so far no systematic comparison or deeper analysis was performed. In pre-clinical and clinical studies mainly RVS CR stimulation was applied (Tass et al., 2012a,b; Adamchic et al., 2014c), while FS CR stimulation was used only in an *in vitro* experiment (Tass et al., 2009). The available results do not allow to judge whether RVS CR or FS CR stimulation or possibly another variant of CR might be superior.

In this study we investigate the efficacy of a new CR stimulation variant for which a sequence is repeated during n stimulation cycles in a row before randomly switching to the next sequence. This type of CR will be called *SVS-n CR stimulation*, where SVS stands for slowly varying sequences. We show that repetition with occasionally switching of the sequence may significantly improve the performance of CR stimulation, leading to a more robust and quicker anti-kindling. To this end, we use a neuronal network model with STDP as described in Section Materials and Methods. The impact of the RVS and the SVS-n CR stimulation are compared in Section Slowly Varying Sequences Boost CR Stimulation Effect. Finally, in Section Optimal Number of Different Sequences Used for SVS CR Stimulation we demonstrate that optimal anti-kindling requires both variation and substantial repetition of the sequence. In fact, a sequence has to be repeated sufficiently often, e.g., at least 25 times, before randomly switching to another sequence.

Materials and Methods

Conductance-Based Hodgkin-Huxley Model

The neural network used in this study consisted of N ($N = 200$) spiking conductance-based Hodgkin-Huxley neurons (Hodgkin and Huxley, 1952). The membrane potential V of each neuron i ($i = 1, \ldots, N$) is characterized by Hansel et al. (1993), Popovych and Tass (2012):

$$\begin{aligned} C\frac{dV_i}{dt} &= I_i - g_{Na} m_i^3 h_i (V_i - V_{Na}) - g_K n_i^4 (V_i - V_K) \\ &\quad - g_l (V_i - V_l) + S_i + F_i. \end{aligned} \tag{1}$$

C is the membrane capacitance, I_i the constant depolarizing current injected into neuron i, S_i is the current that represents synaptic input of the neurons within the network to neuron i and F_i is

the current induced in neuron i by CR stimulation. Values used in this study are: $C = 1\ \mu F/cm^2$, maximum conductance per unit area for the sodium, potassium and leak currents, $g_{Na} = 120$ mS/cm^2, $g_K = 36$ mS/cm^2, $g_l = 0.3$ mS/cm^2, with sodium reversal potential $V_{Na} = 50$ mV, potassium reversal potential $V_K = -77$ mV, leak reversal potential $V_l = -54.4$ mV. For the equations of the time-varying gate variables m, h, and n see Hansel et al. (1993). The injected constant currents (I_i) are uniformly distributed random numbers ($I_i \in [I_0 - \varepsilon_I, I_0 + \varepsilon_I]$, in this study $I_0 = 11.0\ \mu A/cm^2$ and $\varepsilon_I = 0.45\ \mu A/cm^2$) and determine the intrinsic firing rate of the uncoupled neurons.

The coupling term S_i from Equation (1) (Popovych and Tass, 2012) contains a weighted ensemble average of all post-synaptic currents received by neuron i from the other neurons in the network and is given by:

$$S_i = N^{-1} \sum_{j=1}^{N} \left(V_{r,j} - V_i\right) c_{ij} \left|M_{ij}\right| s_j. \tag{2}$$

N is the number of neurons within the ensemble, $V_{r,j}$ is the reversal potential of the synaptic coupling (20 mV for excitatory and –40 mV for inhibitory coupling), and c_{ij} is the synaptic coupling strength from neuron j to neuron i. There are no neuronal self-connections within the network ($c_{ii} = 0$ mS/cm^2). M_{ij} has the form of a Mexican hat (Wilson and Cowan, 1973; Dominguez et al., 2006; De la Rocha et al., 2008) and defines the strength and type of neuronal interaction: strong short-range excitatory $\left(M_{ij} > 0\right)$and weak long-range inhibitory interactions $\left(M_{ij} < 0\right)$. This spatial profile of coupling between neurons i and j is given by:

$$M_{ij} = \left(1 - d_{ij}^2/\sigma_1^2\right) \exp\left(-d_{ij}^2/(2\sigma_2^2)\right) \tag{3}$$

where $d_{ij} = d\left|i - j\right|$ is the distance between neurons i and j,

$$d = d_0/(N-1) \tag{4}$$

is the lattice distance between two neighboring neurons within the ensemble, d_0 is the length of the neuronal chain, $\sigma_1 = 3.5$, and $\sigma_2 = 2.0$ as used in Popovych and Tass (2012). To minimize boundary effects, the neurons form a ring, which implies that $d_{ij} = d \cdot min\left(\left|i - j\right|, N - \left|i - j\right|\right)$.

The synaptic variable s_j in Eqn. 2 is given by:

$$\frac{ds_j}{dt} = \frac{0.5(1 - s_j)}{1 + exp\left[-\left(V_j - 5\right)/12\right]} - 2s_j. \tag{5}$$

Spike Timing-Dependent Plasticity

In general, synaptic coupling strengths change depending on the precise timing of pre- and post-synaptic spikes (Markram et al., 1997; Bi and Poo, 1998). In the present study all synaptic weights c_{ij} were considered to be dynamic variables dependent on the time difference (Δt_{ij}) between the onset of the post- and pre-synaptic spikes t_i, respectively t_j $\left(\Delta t_{ij} = t_i - t_j\right)$. According to the spike timing-dependent plasticity (STDP) rule (Bi and Poo, 1998) the change in synaptic weight is given by:

$$\Delta c_{ij} = \begin{cases} \beta_1 e^{\frac{-\Delta t_{ij}}{\gamma_1 \tau}}, \Delta t_{ij} \geq 0 \\ \beta_2 \frac{\Delta t_{ij}}{\tau} e^{\frac{\Delta t_{ij}}{\gamma_2 \tau}}, \Delta t_{ij} < 0 \end{cases} \tag{6}$$

See Popovych and Tass (2012), In our model we update the synaptic weights c_{ij} in an event-based manner by adding $\delta \cdot \Delta c_{ij}$ for excitatory connections and $-\delta \cdot \Delta c_{ij}$ for inhibitory connections with learning rate $\delta > 0$ every time a neuron spikes. To avoid an unbounded strengthening or weakening, the synaptic weights are restricted to the interval $c_{ij} \in [0, 1]$ mS/cm^2 for excitatory synapses and $c_{ij} \in [0, c_{max}]$ mS/cm^2 for inhibitory synapses with $c_{max} = 1$ unless stated otherwise. In this study the following values are used for the STDP parameters: $\beta_1 = 1$, $\beta_2 = 16$, $\gamma_1 = 0.12$, $\gamma_2 = 0.15$, $\tau = 14$ ms, and $\delta = 0.002$.

Due to STDP and the different intrinsic periods of the neurons, the synaptic weights change constantly. In this study the dynamics of the synaptic weights were investigated on a population level. The strength of the coupling within the neuronal population at time t is given by the synaptic weight averaged over the population:

$$C_{av}(t) = N^{-2} \sum_{i,j} sgn\left(M_{ij}\right) c_{ij}(t), \tag{7}$$

with M_{ij} as defined in Equation (3) and the sign-function sgn. The amount of synchronization of the neuronal activity within the ensemble is influenced by the synaptic weights and can be represented by the order parameter (Haken, 1983; Kuramoto, 1984)

$$R(t) = \left| N^{-1} \sum_j e^{i\varphi_j(t)} \right|, \tag{8}$$

Where $\varphi_j(t) = 2\pi(t - t_{j,m})/(t_{j,m+1} - t_{j,m})$ for $t_{j,m} \leq t < t_{j,m+1}$ is a linear approximation of the phase of neuron j between its m^{th} and $(m+1)^{th}$ spikes at spiking times $t_{j,m}$ and $t_{j,m+1}$. The order parameter R measures the extent of phase synchronization in the neuronal ensemble and takes values between 0 (complete desynchronization) and 1 (perfect in-phase synchronization). For our data analysis the order parameter was averaged over the last 1.6 s of the CR-off period and will be denoted as average order parameter R_{av}.

Coordinated Reset Stimulation Algorithms

Coordinated Reset (CR) stimulation was delivered to the neuronal ensemble of N spiking Hodgkin-Huxley neurons. This was done sequentially via N_s equidistantly spaced stimulation sites (Tass, 2003a): one stimulation site was active during T_s/N_s, while the other stimulation sites were inactive during that period. After that another stimulation site was active during the next T_s/N_s period. All N_s stimulation sites were stimulated exactly once within one stimulation ON-cycle. Therefore, the duration of each ON-cycle is T_s. This spatiotemporal activation

of stimulation sites is represented by the indicator functions $\rho_k(t)$ ($k\epsilon\{1,\ldots,N\}$):

$$\rho_k(t) = \begin{cases} 1, & k^{th}\text{stimulation site is active at } t \\ 0, & \text{otherwise} \end{cases} \quad (9)$$

The stimulation signals induced single brief excitatory post-synaptic currents. The evoked time-dependent normalized conductances of the post-synaptic membranes are represented by α-functions given by Popovych and Tass (2012):

$$G_{stim}(t) = \frac{t - t_k}{\tau_{stim}} e^{-(t-t_k)/\tau}, \quad t_k \le t \le t_{k+1}. \quad (10)$$

Here $\tau_{stim} = T_s/(6N_s)$ denotes the time-to-peak of G_{stim}, and t_k is the onset of the k^{th} activation of the stimulation site. The spatial spread of the induced excitatory post-synaptic currents in the network is defined by a quadratic spatial decay profile (see Popovych and Tass, 2012 for motivation) given as a function of the difference in index of neuron i and the index x_k of the neuron at stimulation site k:

$$D(i, x_k) = \frac{1}{1 + d^2(i - x_k)^2/\sigma_d^2}, \quad (11)$$

with d the lattice distance between two neighboring neurons as defined in Equation (4) and $\sigma_d = 0.08 d_0$ the spatial decay rate of the stimulation current.

The stimulation current from Equation (1) is given by:

$$F_i = [V_r - V_i(t)] \cdot K \sum_{k=1}^{N_s} D(i, x_k)\, \rho_k(t)\, G_{stim}(t), \quad (12)$$

where $V_r = 20\,\text{mV}$ denotes the excitatory reverse potential, V_i the membrane potential of neuron i, K the stimulation intensity, and D, ρ, G are given by Equations (11), (10), and (9).

In this paper we study three different CR algorithms: RVS CR stimulation (Tass and Hauptmann, 2006; Tass and Majtanik, 2006; Popovych and Tass, 2012; Tass and Popovych, 2012), FS CR stimulation (Tass, 2003a,b; Hauptmann and Tass, 2007, 2009; Tass and Hauptmann, 2007, 2009), and our novel SVS CR stimulation. During one sequence each stimulation site is activated exactly once. There are $N_s!$ (in our study 4!=24) different sequences possible to stimulate N_s stimulation sites. In the RVS CR algorithm for each ON-cycle a new sequence was drawn randomly from the set of $N_s!$ possible sequences (see **Figure 1A**). For the slowly varying sequences CR algorithm (SVS-n) the sequence order is random and determined a priori in such a way that each sequence used, is consecutively repeated n times before another one is applied. For the SVS-4 CR stimulation signals as shown in **Figure 1B** one sequence was applied during the first n consecutive ON-cycles. After that the next sequence was applied during the next n consecutive ON-cycles, and so on (see **Figure 1B** for $n = 4$).

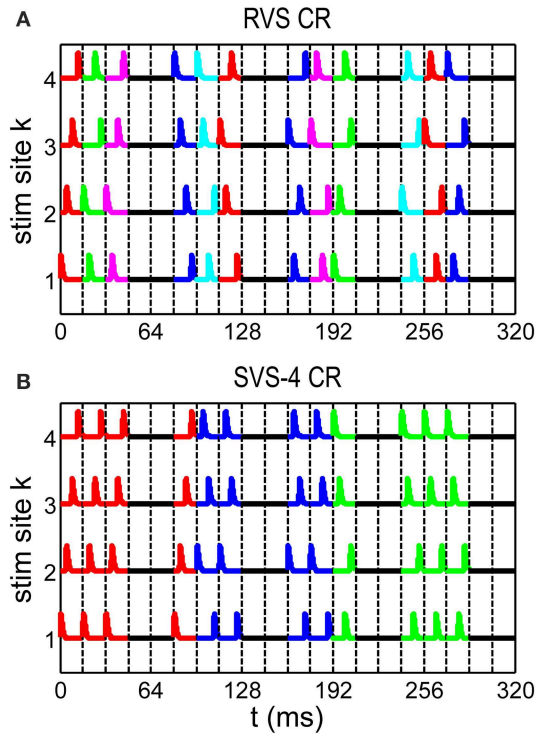

FIGURE 1 | Spatiotemporal stimulation signals of CR stimulation. (A) An example sequence order for the rapidly varying sequences (RVS) CR. **(B)** An example sequence order for the slowly varying sequence CR with every sequence repeated 4 times (SVS-4) before the next sequence is used. A change of color indicates a new sequence. Vertical dashed lines separate stimulation ON- and OFF cycles: three ON-cycles are followed by two OFF-cycles.

Simulation Details and Data Analysis

We ran simulations for different initial network conditions and different sequence orders. For each initial network condition the initial conditions of all N neurons were randomly drawn from uniform distributions ($n_i, m_i, h_i, s_i \in [0, 1]$; $V_i \in [-65, 5]\,mV$; $I_i \in [I_0 - \sigma_I, I_0 + \sigma_I]$). The initial synaptic weights c_{ij} between the neurons were drawn from a normal distribution ($c_{ij} \sim N(\mu = 0.5\mu A/cm^2, \sigma = 0.01\mu A/cm^2)$). After an initial equilibration phase of 2 s, STDP was included for the rest of the simulation. During the first 60 s with STDP the network was given the opportunity to rewire its connections without any influence from an external stimulation. At the end of this STDP-only period the network activity was highly synchronized and the CR simulation was applied for 64 s from $t = 0$ s on. During this CR-on period three stimulation ON-cycles alternated with two OFF-cycles as in the example stimulation signal shown in **Figure 1**. No stimulation was applied during the OFF-cycles. Each ON- and OFF-cycle lasted $T_s = 16$ ms. After 64 s the CR stimulation was stopped permanently and the 64 s lasting CR-off period started. After going through this procedure for one particular stimulation intensity, K, the procedure was repeated from $t = 0$ s on for the other K-values ($K \in \{0.10, 0.20, 0.30 \ldots, 0.60\}$). For each CR stimulation this whole process was repeated for eleven

different initial network conditions and sequence orders. Besides the RVS CR stimulation also the SVS-100 CR stimulations were applied for eleven different combinations of initial conditions and sequence orders. Finally, the optimal number of different sequences used in the SVS CR stimulation was explored.

The resulting values of C_{av} (Equation 7) at $t = 128$ s and R_{av} (Equation 8) averaged over the last 1.6 s of the CR-off period) were plotted in boxplots (Tukey, 1977). In order to compare the results of different CR algorithms for a constant stimulation strength, K, the obtained boxplots are plotted next to each other, whereby the color represents which CR algorithm was used. Statistical significances of differences between the results of the different CR algorithms were determined by the one-sided Mann-Whitney test.

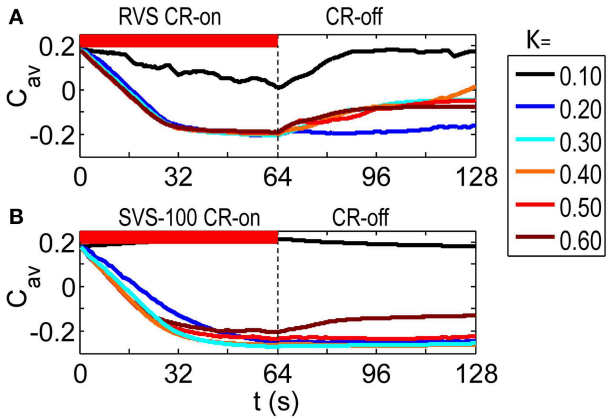

FIGURE 2 | Dynamics of the average synaptic weight, C_{av}, for different stimulation intensities, K. (A) Results of the RVS CR stimulation. **(B)** Results of the SVS-100 CR stimulation. The initial network is the same for all simulations. The sequence order used for each CR method is constant for all K-values. The CR-on period, represented by the red horizontal bar, starts at $t = 0$ s and is switched off at $t = 64$ s (dashed vertical line). During the subsequent 64 s CR-off period, no stimulation is delivered, and C_{av} evolves spontaneously. $c_{max} = 1$ for all simulations.

Results

Slowly Varying Sequences Boost CR stimulation Effect

To verify whether the SVS CR stimulation is more successful than the RVS CR stimulation, the effect of both CR algorithms on the average synaptic weight, C_{av}, as well as on the synchronization of neuronal activity R has to be investigated. Each measure will be explored first for the RVS and then for the SVS CR stimulation.

As visualized in **Figure 2A** the RVS CR stimulation causes a weakening of the average synaptic weight C_{av} during the CR-on period for all stimulation intensities K. At the end of the subsequent CR-off period, the average synaptic weight is still much weaker than before the CR stimulation was applied, except for the weakest stimulation intensity. **Figure 2B** then shows how the SVS CR stimulation, delivered to the same initial network, decreases the average synaptic weights even more and causes in general lower long-lasting C_{av}–values compared to the RVS CR stimulation. Since we are interested in the long-lasting effects of the CR stimulation period, we will concentrate on the values at the end of the CR-off for the remainder of this work.

To investigate whether this observed improvement by the SVS CR stimulation is just a coincidence, we have also changed the sequence order or the initial network conditions. **Figure 3A** shows that by applying another RVS order to the same initial network or by applying the initial sequence order to a network with different initial conditions, different long-lasting C_{av}-values were obtained. Only for the weakest stimulation intensity, $K = 0.10$, the RVS algorithm caused similar long-lasting C_{av}-values. For other stimulation intensities, it suggests that the effect of the RVS CR stimulation depends on the sequence order used and on the initial network conditions. As follows from **Figure 3B**, the success of the SVS-100 CR stimulation depends less strongly on the exact sequence order and the initial network conditions and the SVS-100 CR stimulation results in a smaller C_{av}-value than the RVS CR stimulation, over a wide range of stimulation intensities K continuing the superiority of this method.

Robustness against variations of the sequence order and against initial network conditions is of crucial importance for the CR therapy. Therefore, all stimulations were repeated 11 times for different combinations of initial network conditions and sequence orders. The boxplots in **Figure 4A** show that the long-lasting effect of decreasing the average synaptic strength is significantly better for the SVS-100 than for the RVS CR stimulation over a wide range of stimulation intensities K (one-sided Mann-Whitney test, $p < 0.05$). Besides generating a better C_{av}-value, the SVS CR stimulation is also more robust against initial network conditions and sequence orders. The SVS-100 also induces a significant smaller R_{av} than the RVS CR stimulation (one-sided Mann-Whitney test $p < 0.01$), but for a smaller set of K-values as shown in **Figure 4B**. R_{av} is the value of the order parameter averaged over the last 1.6 s of the CR-off period.

To rule out false estimates of the time averaged order parameter R, *we* used different window lengths. False estimates could, for instance, be caused by low-frequency oscillations of R with periods exceeding the window length used for our averaging analysis. In our analysis of the order parameter R, presented in this paper, we averaged over the last 1.6 s of the 64 s during CR-off period. Averaging R over a quarter (=16 s) of the total CR-off period gave very similar results. Hence, we can consider our results to be sufficiently robust with respect to variations of the length of the time window used for our evaluation.

Simulations for SVS-25 CR stimulation during the 64 s lasting CR-on period gave similar results for C_{av} and R_{av} as the SVS-100 CR (results not shown), illustrating that 25 consecutive repetitions of each sequence are already enough to improve the CR effect.

From the standpoint of clinical applications it is important to understand the relationship between the acute effect achieved during stimulation and the after-effect observed after cessation of stimulation. To this end, we studied the relationship between the values of C_{av} and R_{av} at the end of the CR-on period ($t = 64$ s) and their values at the end of the CR-off period ($t = 128$ s) (**Figure 5**). The relation between C_{av} at $t = 64$ s and at $t = 128$ s

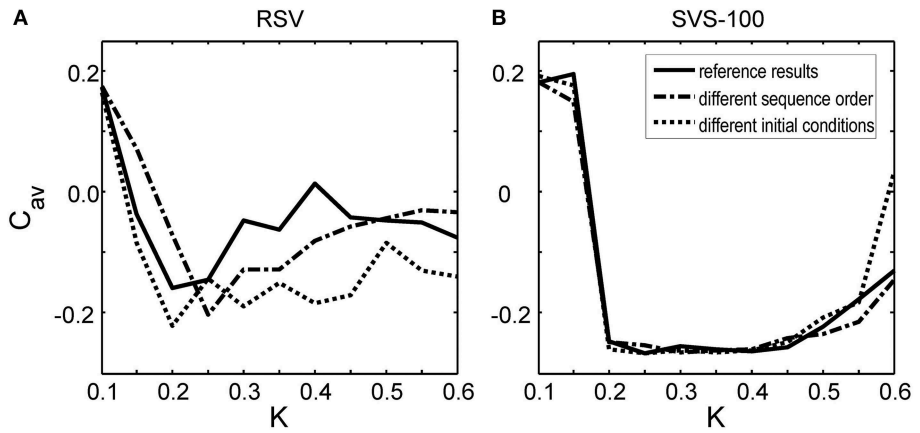

FIGURE 3 | Effect of the sequence order and of the initial network conditions on the average synaptic weight C_{av} at $t = 128$ s as a function of stimulation intensity K. **(A)** C_{av}-values at $t = 128$ s obtained by the RVS CR stimulation. **(B)** C_{av}-values at $t = 128$ s obtained by the SVS-100 CR stimulation. The $C_{av}(t = 128\,\text{s})$ values in **Figure 2** are the reference results and represented by the solid lines in this Figure. The dashed-dotted lines show the result for a simulation with the same initial network conditions as used to obtain the reference results but for another randomly chosen sequence order. The dotted lines represent the obtained C_{av}-values at $t = 128$ s for a simulation with the same sequence order as used to obtain the reference results, but for other initial network conditions.

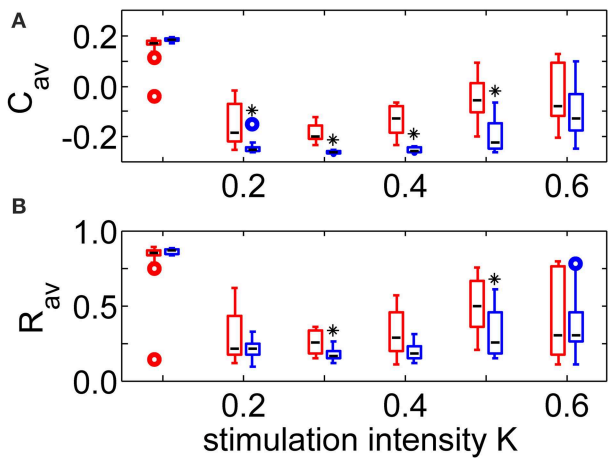

FIGURE 4 | Comparison of the anti-kindling effects at $t = 128$ s for the RVS and the SVS-100 CR stimulation. **(A)** Boxplots of the average synaptic strength, C_{av}, at $t = 128$ s as a function of the stimulation intensity, K, for the RVS and the SVS-100 CR stimulation. **(B)** Boxplots of the order parameter R averaged over the last 1.6 s, R_{av}, as a function of K for the RVS and the SVS-100 CR stimulation. The RVS CR results for the same K-values are shown in red and slightly shifted to the left and the SVS-100 results are shown in blue and slightly shifted to the right. The black lines within the boxes show the medians for each condition, the boxes the middle 50% and the whiskers below (above) the boxes the first (last, respectively) 25%. Outliers are defined as 1.5 times the length of the box below or above the box and represented by open circles. For each condition (K-value and type of CR) the simulations are repeated eleven times for different initial conditions of the network in combination with different sequence orders. One asterisk indicates a significantly lower C_{av} - or R_{av}-value compared to the values obtained by the RVS CR stimulation (one-sided Mann-Whitney test with $p < 0.05$).

is visualized in **Figure 5A**. In a first approximation, small values C_{av} and R_{av} at $t = 64$ s are required but not necessarily sufficient for small values of C_{av} and R_{av} at $t = 128$ s. Hence, with a certain probability a pronounced acute stimulation effect is associated with a good long-term outcome. In contrast, poor acute stimulation effects are not related to pronounced after-effects.

Optimal Number of Different Sequences Used for SVS CR Stimulation

In this section we analyze the impact of sequence changes on the dynamics of the average synaptic connectivity as assessed by C_{av}. To this end, first, we perform a CR stimulation with fixed sequence (FS CR) and compare it to CR stimulation epochs where the sequence is either changed once or at three equidistant times without changing the total duration of the CR-on period. This implies that the number of different sequences multiplied with the number of consecutive repetitions, n, is constant. Finally, the optimal number of different sequences used in the SVS CR stimulation was explored.

We analyzed the effect of *FS CR stimulation* for eleven different initial network conditions in combination with a different sequence for each network, respectively. **Figure 6A** clearly shows that for the FS CR stimulation (SVS-2400) with $K = 0.20$, the decrease of C_{av} strongly depends on which sequence is used. Pronounced long-lasting effects are achieved by some sequences, whereas no anti-kindling is observed for other sequences. Increasing the stimulation intensity to $K = 0.45$ improves the robustness of FS against the choice of the sequence used and the initial network conditions (**Figure 6B**). For $K = 0.45$ the average synaptic weight stabilizes at a small to intermediate value, depending on the sequence and the initial network conditions. The stabilization of C_{av} is more rapidly achieved at higher stimulation intensity K.

By using *two different sequences* instead of just one sequence, the first sequence may stabilize C_{av} at an intermediate value of C_{av} and, hence, lead to a sub-optimal outcome. However, at $t = 32$ s the second sequence takes over, and may further reduce C_{av} as

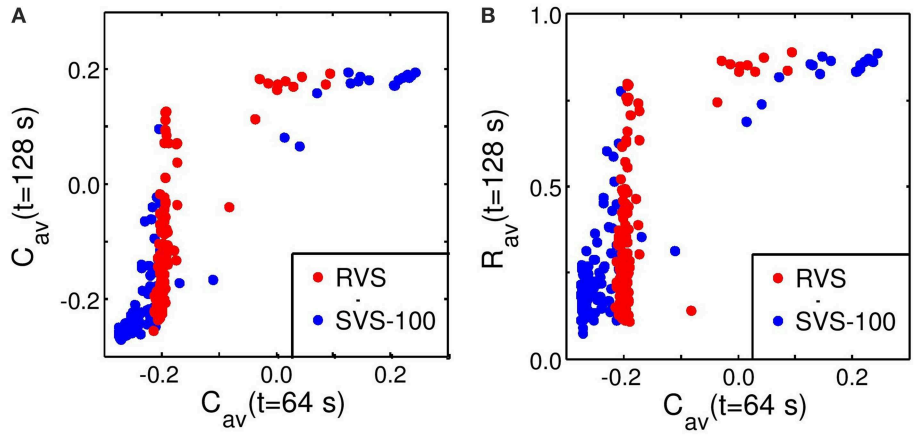

FIGURE 5 | Predictability of the anti-kindling effect by C_{av} at $t = 64$ s. (A) Relation between C_{av} at the end of the CR-on period ($t = 64$ s) and at the end of the CR-off period ($t = 128$ s). **(B)** Relation between C_{av} at the end of the CR-on period ($t = 64$ s) and R_{av} at the end of the CR-off period ($t = 128$ s). The C_{av}-values at $t = 64$ s are calculated and plotted against C_{av} or R_{av} at $t = 128$ s for each condition (initial network conditions, stimulation intensity, sequence order, $c_{max} = 1$) as used for **Figure 4**. Red circles represent the results of the RVS CR stimulation, blue circles of the SVS-100 CR stimulation. Note that the red circles are plotted on top of the blue circles.

shown by its kinks at $t = 32$ s (**Figure 6C** for $K = 0.20$ and SVS-1200), in particular, for the more effective stimulation intensity $K = 0.45$ (**Figure 6D**).

By the same token, the long-lasting effects on the mean synaptic connectivity C_{av} and the robustness of the stimulation further improve by using *four different sequences* (SVS-600, **Figure 6E** for $K = 0.20$ and **Figure 6F** for $K = 0.45$). Again, especially at higher stimulation intensity changes of the sequence may come with a stepwise-like further reduction of C_{av} showing up as kinks in the time course of C_{av} at times when sequences are changed ($t = 16$, 32, and 48 s).

Analogously, we further increase the number of different sequences used during one CR epoch. **Figure 7** shows the stimulation outcome in terms of synaptic connectivity C_{av} (**Figures 7A,C**) and order parameter R_{av} (**Figures 7B,D**) averaged over the last 1.6 s of the CR-off period for different stimulation intensities ($K = 0.20$ in **Figures 7A,B** and $K = 0.45$ in **Figures 7C,D**). The statistics obtained from a set of eleven simulations performed for different initial network conditions and sequence orders shows that the main part of the SVS-induced improvement of the CR effect is already achieved with four different sequences. Using more than four different sequences hardly leads to a further reduction of R_{av} and C_{av} and their variability.

Discussion

Our results show that the SVS CR stimulation leads to significantly weaker average synaptic weights than the RVS CR stimulation over a wide range of stimulation. Within this range the Inter-Quartile-Range (25th to 75th percentile) is smaller for the SVS CR approach compared to the RVS CR. This implies that the SVS CR approach is more robust against initial conditions of the network and against the order of the sequences than the RVS CR in this range. The differences between the results of the SVS with 25 and 100 consecutive repetitions of each sequence are in general not significant, although more repetitions tend to have a larger impact on the average synaptic weight (results not shown). A more significantly reduced average synaptic weight does not necessarily translate into more significantly reduced overall synchrony. In fact, for the SVS CR stimulation the network activity was significantly more desynchronized than for the RVS CR stimulation in a smaller range of stimulation intensities than for the weakening of the network connectivity.

Optimal anti-kindling is obtained at intermediate stimulation intensities (**Figures 3**, **4**). This is in agreement with previous computational studies (e.g., Lysyansky et al., 2011a; Popovych and Tass, 2012; Ebert et al., 2014). On the one hand CR stimulation has to be of sufficient intensity to achieve phase resets of the different subpopulations, but on the other hand at high intensities the subpopulations are no longer separately stimulated. In the limiting case of very high intensities each stimulus affects nearly the whole neuronal population and causes an entrainment of the whole population which fosters synchronization rather than desynchronization. Our results are stable with respect to variations of model parameters, e.g., by doubling the maximum allowed inhibitory synaptic weight ($c_{max} = 2$ for inhibitory synapses, results not shown).

Our results show that optimal long-lasting desynchronization requires the right combination of appropriate repetition and occasional variation of sequences. In fact, SVS-CR stimulation is better than FS CR stimulation over a wide range of stimulation intensities. Furthermore, the optimal number of different sequences for the SVS CR stimulation is four or more. This implies that repetition alone, like in the case of FS CR simulation (Hauptmann and Tass, 2007, 2009; Tass and Hauptmann, 2007, 2009; Tass et al., 2009), is not the only ingredient for the improvement of CR stimulation. With insufficiently many different sequences in the SVS CR approach, the network can stabilize in a local minimum that is much larger than the global minimum C_{av}-value for a given stimulation intensity. In

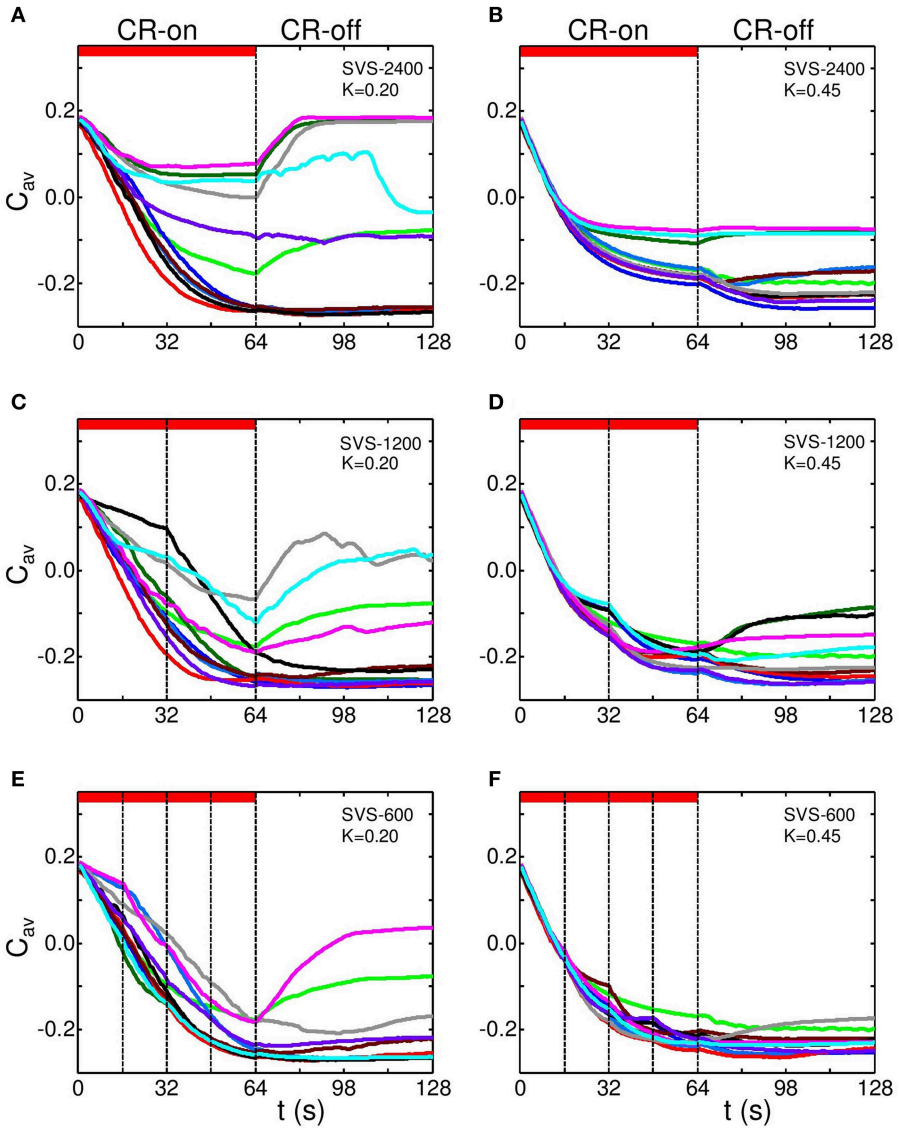

FIGURE 6 | Effect of switching the sequence during CR stimulation. In a series of simulations with different stimulation intensities ($K = 0.20$ in left panels and $K = 0.45$ in right panels) the sequence was either kept fixed [FS CR stimulation, **(A,B)**], randomly varied just once [in the middle of the stimulation period, at $t = 32$ s, **(C,D)**] or randomly varied at three equidistant times [at $t = 16$, 32, 48 s, **(E,F)**]. Simulations were performed for eleven different sequence orders and initial network conditions. Each panel shows the dynamics of C_{av} for each of the eleven simulations in a different color. FS CR stimulation **(A,B)**: Time course of C_{av} for eleven combinations of different initial network conditions and different sequence for SVS-2400, respectively, for $K = 0.20$ **(A)** and $K = 0.45$ **(B)**. Change of sequence in the middle of the stimulation epoch **(C,D)**: Two different sequences, each applied 1200 times in a row. Change of sequence at $t = 32$ s, with $K = 0.20$ **(C)** and $K = 0.45$ **(D)**. Sequence is changed three times at equidistant times ($t =$, 16, 32, and 48 s) during the stimulation epoch **(E,F)**: In each simulation four different sequences are applied 600 times in a row, so that after 16 s the next sequence randomly chosen, with $K = 0.20$ **(E)** and $K = 0.45$ **(F)**. The red horizontal bars represent CR-on periods. The vertical dashed-dotted lines indicate a change of sequence. $c_{max} = 1$ in all simulations.

case the sequence is replaced after many repetitions by another sequence and again after a large number of repetitions by another sequence, the network connectivity can stepwise decrease from one local minimum to another, in this way, approaching the global minimum for a given stimulation intensity. Using more than four different sequences in the SVS CR stimulation does not significantly improve the long-lasting anti-kindling effects compared to those obtained with just four different sequences. The different local minima correspond to different attractors of the network (see Popovych et al., 2015). In fact, in our model network a multitude of attractors with different amount of mean synaptic weight and neuronal synchrony coexist, covering the whole spectrum from minimal mean connectivity and synchrony up to strongly up-regulated mean connectivity and synchrony. Hence, our results indicate that SVS CR stimulation prevents the network from getting stuck in undesirable attractors (with

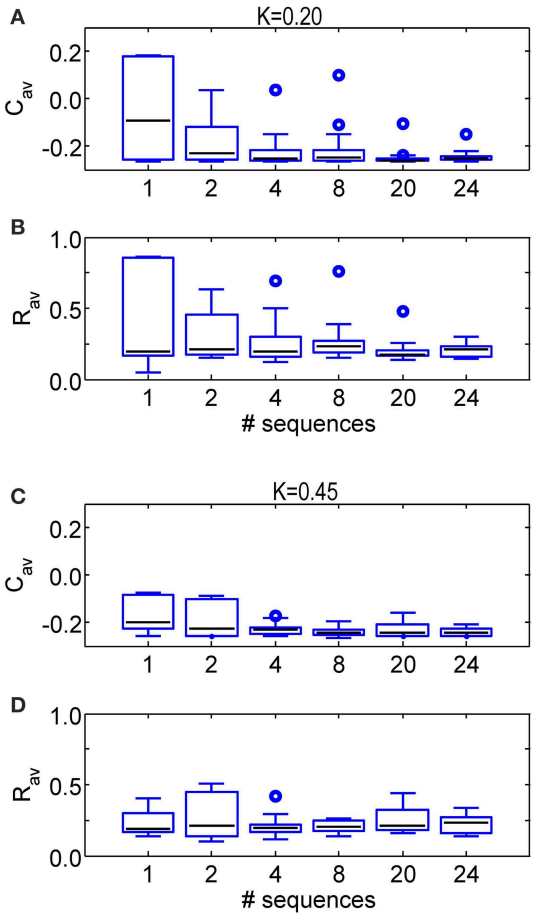

FIGURE 7 | Comparison of the anti-kindling effects for some numbers of different sequences applied during the SVS CR stimulation. (A) Boxplots of C_{av} at $t = 128$ s for different numbers of sequence changes used in the SVS CR stimulation with $K = 0.20$. **(B)** Boxplots of R_{av} at $t = 128$ s for some numbers of different sequences used in the SVS CR stimulation with $K = 0.20$. **(C)** As in **(A)** for $K = 0.45$. **(D)** As in **(B)** for $K = 0.45$. The black lines within the boxes show the medians for each condition, the boxes the middle 50% and the whiskers below (above) the boxes the first (last, respectively) 25%. Outliers are defined as 1.5 times the length of the box below or above the box and represented by open circles. For each condition (K-value and number of sequences) the simulations are repeated eleven times for different initial conditions of the network in combination with different sequence(s). The number of consecutive sequence repetitions was adjusted with respect to the number of different sequences so that the duration of the CR-on period is always 64 s for each simulation. For example if two different sequences are used, each of them is repeated 1200 times in a row, in case four different sequences are used, each of them is repeated 600 times.

intermediate mean connectivity and synchrony) in the course of the anti-kindling stimulation.

Another difference between the SVS-100 and the RVS CR stimulation is that for the SVS CR stimulation by definition in a suitably large time window each sequence is repeated exactly 100 times, but that for the RVS CR stimulation the number of (timely separated) repetitions of each sequence can vary within such a time window, since by definition the sequence of the RVS CR changes from ON-cycle to ON-cycle, where each sequence occurs with equal probability. For an infinitely long time window also for the RVS CR stimulation the different sequences will occur with equal probability. However, on the time scale of one completed series of sequences of the SVS-100 CR stimulation, i.e., for larger, but not infinitely large numbers of sequences, this may be different. Taking a permutation of all 2400 applied sequences (including the repeated sequences) of a SVS-100 CR stimulation generates a CR stimulation signal in which the different sequences occur randomly, but each still exactly 100 times. Simulations with this permutated CR stimulation signal show that C_{av} and R_{av}-values are similar to those obtained by the RVS CR stimulation although the spread is in general larger for the permutated than the random signal (results now shown). This suggests that a constant frequency with which each sequence occurs in a wider time window does not contribute to the success of the SVS CR stimulation, but that it is mainly determined by the consecutive repetitions of a sequence and the number of different sequences. This is actually supported by the fact that already four different sequences in the SVS CR stimulation are sufficient to induce a full-blown anti-kindling (see above).

Applying our SVS CR approach to DBS may be particularly rewarding, since with the same stimulation intensity as used for RVS CR or fixed sequence CR, SVS CR might lead to a better therapeutic outcome. Reducing the stimulation energy will likely lead to a reduction of the rate of side effects. RVS CR DBS was successfully applied at stimulation amplitudes (of the single stimulation pulses) similar to those of standard permanent high-frequency DBS (Adamchic et al., 2014a) as well as corresponding to a third of the amplitude used for standard permanent high-frequency DBS (Tass et al., 2012a). Accordingly, within that range of stimulation amplitudes SVS CR-DBS might be superior to RVS CR-DBS. However, given the intensity dependence of the anti-kindling effects (e.g., **Figure 4**), systematic dose finding studies for both types of CR-DBS are required to best exploit their actual clinical potential. By the same token, systematic dose finding studies should be conducted for acoustic CR stimulation for the treatment of tinnitus (Tass et al., 2012b) for SVS CR. As yet, acoustic RVS CR stimulation was delivered at only one stimulation intensity (i.e., loudness level), namely for just super threshold loudness. In the context of dose finding studies the results from **Figure 5** might be important, since they show that—at least in the model under study—acute effects (achieved during stimulation) are necessary but not sufficient for pronounced long-term desynchronization effects observed after cessation of stimulation.

In a previous computational study it was shown that FS CR stimulation may augment brain function by counteracting cerebral hypo-activity without promoting pathological neuronal synchrony (Lysyansky et al., 2011b). Accordingly, a forthcoming study might focus on the comparison of the potential of SVS CR for activating brain areas and protecting the brain from abnormal synchrony and kindling as opposed to both FS CR and RVS CR.

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Conflict of Interest Statement: Peter Tass is employed by Jülich Research Center and works as consulting professor at Stanford University. Formerly working with ANM GmbH (Cologne, Germany) and shareholder of ANM GmbH. Several patents protect invasive and non-invasive CR neuromodulation stimulation. The main inventor of the CR patent portfolio is Peter Tass, the assignee is Jülich Research Center. Magteld Zeitler is working at Jülich Research Center. Peter Tass and Magteld Zeitler are co-inventors of recently filed SVS CR patents.

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Compensation or Restoration: Closed-Loop Feedback of Movement Quality for Assisted Reach-to-Grasp Exercises with a Multi-Joint Arm Exoskeleton

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Assistive technology allows for intensive practice and kinematic measurements during rehabilitation exercises. More recent approaches attach a gravity-compensating multi-joint exoskeleton to the upper extremity to facilitate task-oriented training in three-dimensional space with virtual reality feedback. The movement quality, however, is mostly captured through end-point measures that lack information on proximal inter-joint coordination. This limits the differentiation between compensation strategies and genuine restoration both during the exercise and in the course of rehabilitation. We extended in this proof-of-concept study a commercially available seven degree-of-freedom arm exoskeleton by using the real-time sensor data to display a three-dimensional multi-joint visualization of the user's arm. Ten healthy subjects and three severely affected chronic stroke patients performed reach-to-grasp exercises resembling activities of daily living assisted by the attached exoskeleton and received closed-loop online feedback of the three-dimensional movement in virtual reality. Patients in this pilot study differed significantly with regard to motor performance (accuracy, temporal efficiency, range of motion) and movement quality (proximal inter-joint coordination) from the healthy control group. In the course of 20 training and feedback sessions over 4 weeks, these pathological measures improved significantly toward the reference parameters of healthy participants. It was moreover feasible to capture the evolution of movement pattern kinematics of the shoulder and elbow and to quantify the individual degree of natural movement restoration for each patient. The virtual reality visualization and closed-loop feedback of joint-specific movement kinematics makes it possible to detect compensation strategies and may provide a tool to achieve the rehabilitation goals in accordance with the individual capacity for genuine functional restoration; a proposal that warrants further investigation in controlled studies with a larger cohort of stroke patients.

Keywords: robot-assisted rehabilitation, stroke rehabilitation, hemiparesis, motor recovery, upper-limb outcome assessment

INTRODUCTION

Assistive rehabilitation technology allows an increase and standardization in the amount of upper limb movement therapy after stroke, potentially resulting in improved arm/hand function and muscle strength, albeit respective trials have, as yet, provided only low-quality evidence (Kwakkel et al., 2008; Mehrholz et al., 2015). In clinical settings, therapists often provide the patient with feedback on the movement quality to encourage relearning of premorbid movement patterns (Cirstea and Levin, 2007). Particularly in patients with severe impairment, deficits in the range and coordination of elbow and shoulder movements might interfere with reaching performance (Cirstea and Levin, 2000; Cirstea et al., 2003). Moreover, motor compensation could limit gains in motor function by learned non-use and lead to pain and joint contractures in the long run (Cirstea and Levin, 2007). However, although robot-assisted therapy focuses on task performance, it usually does not differentiate between compensation strategies and genuine motor restoration despite being capable of objective movement evaluation (Kwakkel et al., 2008). Although kinematic parameters would be particularly suitable for assessing movement quality during rehabilitation exercises, current robotic devices tend to capture end-point measures that lack information on proximal interjoint coordination (Nordin et al., 2014) which would be necessary to differentiate recovery from compensation. In this context, a gravity-compensating multi-joint exoskeleton could not only support reach-to grasp movements in severely affected stroke patients but also provide closed-loop virtual reality feedback of movement quality during task-oriented training. This pilot study intended to explore the methodological feasibility and clinical validity of virtual reality visualization and closed-loop feedback of joint-specific movement kinematics to capture the evolution of upper extremity movement patterns in severely affected stroke patients. We furthermore wanted to quantify the individual degree of natural movement restoration or compensation for each patient. When a proof-of-concept is demonstrated here, such an approach would provide a tool to follow rehabilitation goals in accordance with the individual capacity for genuine functional restoration, a strategy that could then be verified by further investigations in controlled studies.

MATERIALS AND METHODS

We recruited ten right-handed healthy subjects (6 males, mean age: 29 ± 4 [24 39] years) and three right-handed stroke patients (all male, mean age: 62 ± 6 [56 68] years). The patients were in the chronic phase after stroke (57 ± 22 [34 78] months) and presented with a severe and persistent hemiparesis of the left side. To ensure that our results were comparable to earlier studies, *coordination*, *speed* and *reflexes* were not taken into account. This resulted in a modified upper extremity Fugl-Meyer-Assessment scores (UE-FMA) of 12, 12, and 25, respectively. This study was in accordance with the guidelines of the ethic committee of the local medical faculty. Participants performed either a single session (healthy control group) or 20 sessions in the course of 4 weeks (patients) of reach-to-grasp training with a multi-joint exoskeleton attached to the left arm. The orthosis was calibrated according to the individual anatomy (e.g., shoulder position, forearm/upper arm length) of each patient. This setup and calibration of the system before every session took about 5 min per patient. Each session lasted approximately 30 min and consisted of 150 trials. The general experimental setup has already been described in detail elsewhere (Grimm and Gharabaghi, 2016; Grimm et al., under review) and is cited here when applied in the same way.

Exoskeleton and Virtual Reality

We used a commercially available (Armeo Spring, Hocoma, Volketswil, Switzerland) rehabilitation exoskeleton for shoulder, elbow and wrist joints with seven axes (i.e., degrees of freedom) providing antigravity support for the paretic arm and registration of movement kinematics and grip force. This device allowed individual adjustments e.g., of gravity compensation, thereby supporting patients with severe impairment in performing task-oriented practice within a motivating virtual environment. Kinematic sensor data was provided by 7 built-in angle sensors (sensor resolution $<0.2°$) for shoulder flexion/abduction (1 sensor), shoulder rotation (2 sensors), elbow flexion/extension (1 sensor for horizontal registration, 1 sensor for vertical registration), forearm pronation/supination (1 sensor) and wrist flexion/extension (1 sensor). The shoulder rotation was calculated as the sum of the two sensors. The upper arm movement was calculated as the angle between forearm and upper-arm in three-dimensional space. The sensors were placed directly in the movement axis of the exoskeleton within the joints, allowing an accurate registration of the actual joint position of the upper arm, forearm and hand (**Figure 1**). Kinematic data of hand closure/opening could not be captured directly with this set up. We therefore estimated the hand function indirectly by registering the grip force. Grip force has previously been shown to correlate with motor function in chronic stroke patients (Boissy et al., 1999) and was captured with an in build mid-palmar grip pressure sensor in the present study.

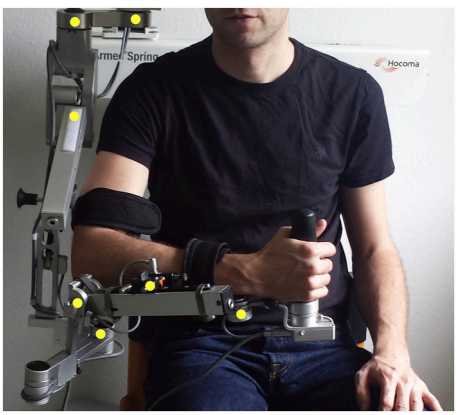

FIGURE 1 | Exoskelleton setup and location of angle sensors within the device (yellow dots).

Thereby, a complete real-time registration of the subject's kinematic reach-to-grasp movement could be performed with the orthosis. We extended these features in-house by using the real-time sensor data of the exoskeleton to display a three-dimensional multi-joint visualization of the user's arm in virtual reality (**Figure 2A**). The exercises where displayed to the subjects on a monitor in front of the setup. For this purpose, we captured the angles of all arm joints and the grip force from a shared memory block using a file mapping communication protocol. The virtual arm engine was programmed in a Microsoft XNA™ framework. The arm model utilized by the engine was constructed as a meshed bone-skin combination with 54 bones (3Ds Max 2010™, Autodesk). The measured joint angles and grip forces of the device were used to modify the bone-vectors of the meshed model according to the movements of the user thereby providing online closed-loop feedback. The kinematic data and the 3D virtual representation were updated in 20 ms intervals. The joint angles of the exoskeleton were directly represented in virtual reality, whereas the grip forces were augmented to feedback natural hand function. Prior to each session, participants were instructed to perform a natural reach-to-grasp movement during the task by using distal (elbow) rather than proximal (shoulder) movements. The participants were moreover encouraged to track and adjust their movements accordingly with the information provided by the virtual environment. Furthermore, they were informed that their movement quality would be captured and evaluated afterwards. This preparation was intended to prime the participants to exploit the information provided by the virtual feedback. The three-dimensional visualization of the arm was then applied during each task as an implicit online feedback of movement quality, since explicit information can disrupt motor learning in stroke patients (Boyd and Winstein, 2004; Cirstea and Levin, 2007). Various virtual training paradigms were designed to allow for different rehabilitation exercises resembling activities of daily living.

Task Design

In this study, participants performed a reach-to-grasp movement toward a ball which changed its position in virtual space after each trial, necessitating three-dimensional transfer movements. The ball had to be grasped, carried to a distant basket and then released again (**Figure 2B**). The virtual hand could interact with the ball as soon as it entered a defined range around the latter. The ball changed its color according to the hand position (white: out of range, green: possible to grasp, yellow: possible to transfer, red: possible to release). The grasping and releasing of the virtual ball was performed by applying force to the grip sensor and opening the hand, respectively, while the threshold was adjusted to the individual strength of the user. No other support was provided during the exercises. The level of orthotic assistance remained constant in the course of the 20 sessions.

Outcome Measures

The kinematic assessment included both motor performance and movement quality (Nordin et al., 2014). The motor performance was estimated with regard to accuracy, temporal efficiency and range of motion. Movement accuracy, more specifically the decrease of inaccuracy, was captured by calculating changes of movement direction along an optimal path toward the targets, by estimating the distance function between the hand-position and the final endpoint, and by calculating the second derivative of the function to acquire the number of turning points for each task (Cirstea et al., 2006). Temporal efficiency was captured as the mean velocity of the hand between the targets while calculating their distance for X-, Y- and Z-directions in virtual units (vu). The range of motion of each joint was measured according to the orthosis and displayed in degrees along with the mean change in grip pressure. Movement quality of proximal inter-joint coordination was defined as the amount of compensatory shoulder inward rotation during the task and quantified by a shoulder/elbow index, i.e., the degree of inward rotation of the shoulder in relation to the degree of elbow movement. More specifically, a larger proportion of shoulder movement would indicate compensation, while a larger proportion of elbow movement for the same task would indicate a rather natural movement.

Statistics

Statistical analysis was performed on a Matlab 2010b Engine. Data was tested for linear distribution using the Lilliefors-test (2-sided goodness-of-fit test). The non-parametric Kruskal–Wallis was used for group comparisons. To estimate the evolution of parameters during training, a robust multilinear regression model was fitted. Although the Lilliefors-test revealed normality of the data, a robust multilinear regression analysis was applied in order to minimize the impact of outliers. The fitting function was

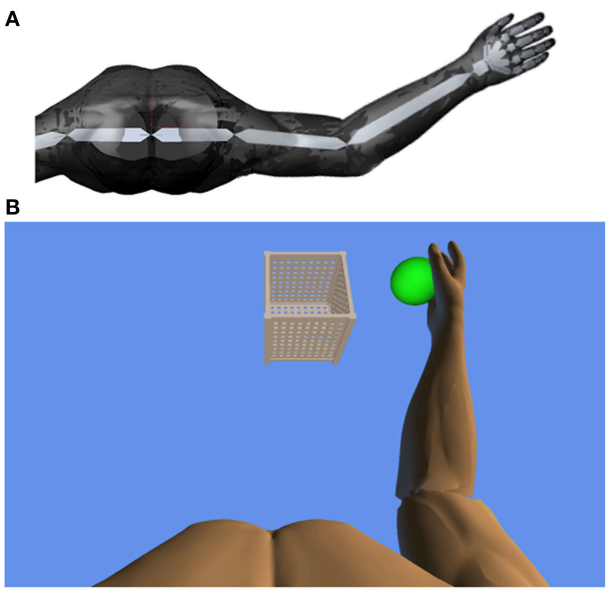

FIGURE 2 | (A) Bone architecture of the three-dimensional multi-joint visualization of the user's arm in virtual reality. **(B)** Virtual training environment for reach-to-grasp movements toward a ball which changes its position in space after each trial. The ball has to be grasped, carried to a distant basket and then released again.

TABLE 1 | Overview of kinematic data for subjects and patients, respectively.

Parameter	Subjects	Patients	*p*-value
Inaccuracy, number of turning points	4.20 ± 0.42 [4.00 5.00]	8.75 ± 2.51 [6.00 13.00]	<0.001
Average velocity (distance/time) (vu/s)	13.86 ± 2.17 [11.31 17.53]	3.89 ± 1.85 [0.90 8.04]	<0.001
Grip pressure	0.45 ± 0.19 [0.14 0.69]	0.684 ± 0.27371 [0.22 1.04]	<0.001
Shoulder movement, angle in degrees (°)	32.90 ± 8.03 [21.81 44.42]	22.00 ± 12.48 [11.93 35.97]	<0.001
Elbow movement, angle in degrees (°)	36.83 ± 7.65 [19.65 44.79]	19.18 ± 5.03 [6.94 28.87]	<0.001
Shoulder/elbow index	0.78 ± 0.05 [0.71 0.88]	1.36 ± 0.30 [1.0 1.58]	<0.001

TABLE 2 | Individual slopes of robust multilinear regression models of kinematic changes in the three stroke patients (n.s.: not significant).

Parameter	Patient 1	Patient 2	Patient 3
Inaccuracy, turning points	−0.24, $p = 0.26$ (n.s.)	−0.14, $p = 0.02$	−0,06, $p < 0.001$
Average velocity (distance/time) (vu/s)	+ 0.14e-3, $p < 0.001$	+ 0.13e-3, $p < 0.001$	+ 0.17e-3, $p < 0.001$
Grip pressure	+1.1e-3, $p = 0.08$ (n.s.)	+4.4e-3, $p < 0.001$	+8.4e-3, $p < 0.001$
Shoulder movement, angle in degrees (°)	+0.14, $p = 0.45$ (n.s.)	+0.4, $p = 0.01$	+1.2, $p < 0.001$
Elbow movement, angle in degrees (°)	+0.49, $p = 0.01$	+0.36, $p = 0.01$	+0.36, $p < 0.001$
Shoulder/elbow index	−27e-3, $p = 0.007$	−15e-3, $p = 0.05$	−6e-3, $p = 0.46$ (n.s.)

based on an iteratively reweighted least squares algorithm. The weights of each iteration were calculated by applying a bisquared function to the residuals of the previous iteration. For every fitting function the slope b of coefficient estimates was presented. The significance level was set to $p = 0.05$ for all tests.

RESULTS

Patients differed significantly with regard to motor performance (accuracy, temporal efficiency, range of motion) and movement quality (proximal inter-joint coordination) from the healthy control group (**Table 1**). Most notably, they applied compensatory strategies by using more shoulder than elbow movements.

However, the patients showed motor learning in the course of the training program with significant changes in most kinematic measures toward the reference parameters of healthy participants (**Table 2**) paralleled by improved FMA-UA scores (+1, +2, +5 points, respectively) in the end of the training.

Most importantly, the evolution of movement pattern kinematics of the shoulder and elbow enabled us to quantify the individual degree of natural movement restoration for each patient: Patient 1 had the lowest scores in all kinematic parameters and also showed the poorest motor performance (**Figure 3**). However, he presented with the steepest evolution of movement quality and was the only patient to reach the reference parameter of healthy participants (**Figure 4**). By contrast, patient 3 showed the highest kinematic parameters, i.e., the best motor performance (**Figure 3**), but also revealed the strongest compensatory movements with the shoulder (**Figure 4**).

DISCUSSION

Rehabilitation devices with a gravity-compensating arm exoskeleton provide assistance for intensive exercises in severely affected stroke patients and may thereby improve motor performance in the course of a training intervention (Housman et al., 2009). However, functional gains in hemiparetic patients are often achieved by non-physiologic movements with a disturbed shoulder-arm inter-joint coordination (Levin, 1996; Levin et al., 2002). Although these compensatory strategies might be efficient in short-term task accomplishment, they may lead to long-term complications such as pain and joint-contracture (Cirstea and Levin, 2007). Movement pattern kinematics may provide accurate, valid, reproducible and predictive measures of the impairment severity in chronic stroke (Subramanian et al., 2010) and of atypical movement patterns that aim to compensate the diminished range of motion of the affected limb (Cirstea and Levin, 2000). In this context, providing detailed information about how the movement is carried out, i.e., the movement quality regarding inter-joint coordination, is more liable to recover premorbid movement patters and to avoid compensatory movements than to provide information about movement outcome, i.e., end-point based accuracy information, only (Cirstea et al., 2006; Cirstea and Levin, 2007). When this feedback is administered during virtual reality training, even less compensation was achieved in the moderate-to-severe group (Subramanian et al., 2013). However, in these previous studies, information on movement quality was provided *explicitly* to the patients via auditory feedback. Moreover, all patients who received this feedback on their movement pattern kinematics were *mildly or moderately-to-severely* affected and were able to perform reach-to-grasp movements without assistance.

In the present feasibility study, we extended this line of research by incorporating information on movement quality as *implicit* closed-loop feedback in the virtual environment of an exoskeleton-based rehabilitation device suitable for *severely affected* stroke patients who require gravity-support to perform activities of daily living such as reach-to-grasp exercises. Notably, antigravity-support did not interfere with the

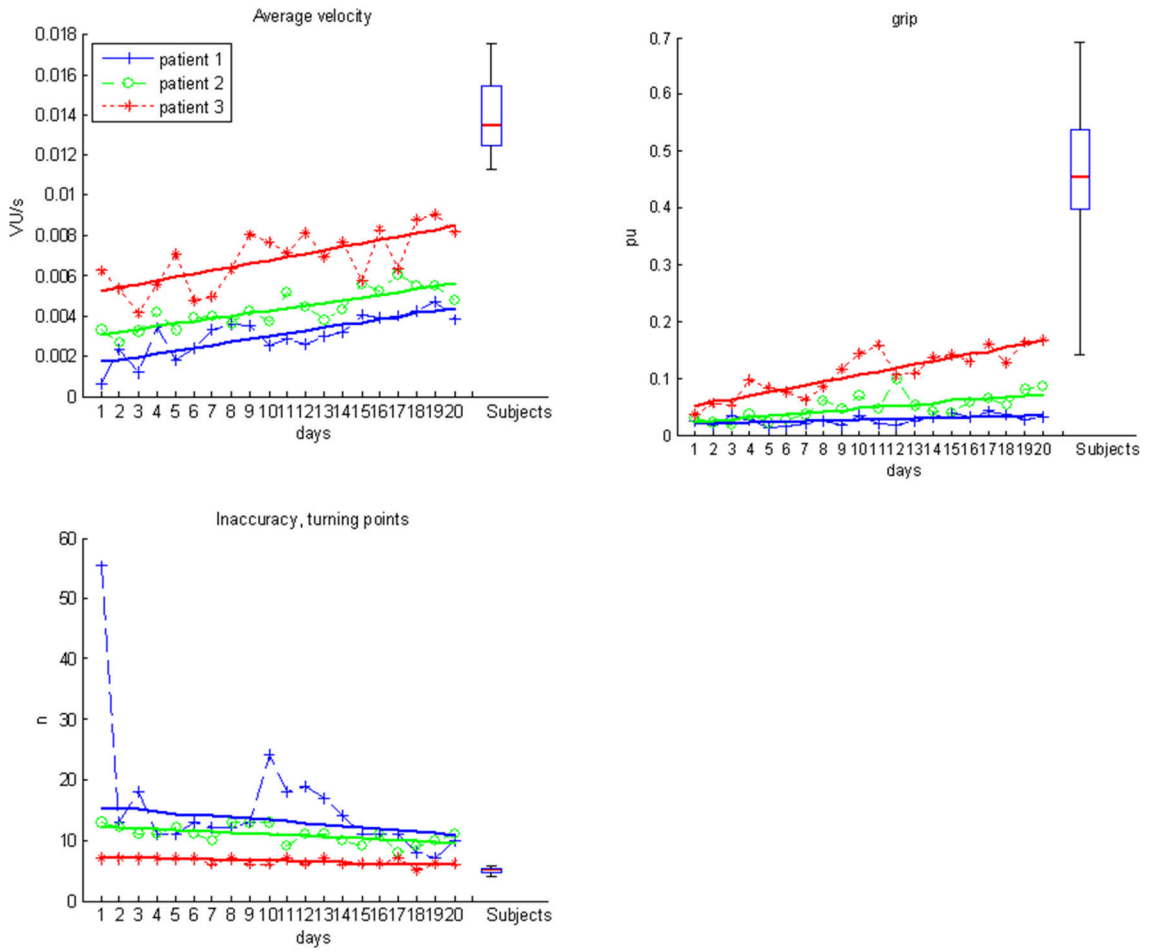

FIGURE 3 | Motor performance data for subjects (boxplots) and individual patients over the time course of training.

kinematic evaluation of proximal inter-joint coordination. By contrast, this approach allowed disentangling in patients with severe impairments whether improved motor performance was achieved by compensation or by functional restoration. Notably, improvement in kinematic measures may be misleading since driven by compensatory strategies. The observations of this study highlighted that these measures were not sufficient to fully assess the evolution during motor rehabilitation thereby supporting the analysis of multi-joint information along the movement trajectory. Moreover, the continuous visual feedback of the whole arm kinematics allowed the patients to adjust their movement quality online during each task; an approach closely resembling natural motor learning. Although pathological measures improved significantly toward the reference parameters of healthy participants, this study did not provide evidence for the specificity of these effects to the implemented setup, i.e., feedback modality. Future studies need therefore to address this question by directly comparing multi-joint with end-effector feedback in controlled trials with long-term follow up evaluation, before conclusions about the therapeutic superiority of the presented approach can be drawn. In any case, however, the diagnostic advantage of detecting compensatory strategies (i.e., use of proximal instead of distal joints in a reach-to-grasp task) with the help of the multi-joint orthosis remains evident.

Future studies may explore the additional effects of brain stimulation on movement quality for assisted reach-to-grasp exercises: a recent study which applied bilateral transcranial direct current stimulation has demonstrated improved motor performance beyond the natural learning curve while using the very same multi-joint arm exoskeleton studied in the present work (Naros et al., 2016a). Moreover, brain state-dependent transcranial magnetic stimulation has been demonstrated to induce robust increases of corticospinal excitability (Kraus et al., 2016b) and may thereby amplify use-dependent plasticity when applied in conjunction with orthotic rehabilitation devices (Gharabaghi, 2015). Future approaches may also address patients with even more limited residual motor function as well (which might not benefit from the presented approach) by providing closed-loop feedback with a *robotic* multi-joint exoskeleton during brain-states in which both the participant's effort to move and the responsiveness of the brain for peripheral input are reflected (Brauchle et al., 2015). In such a restorative framework,

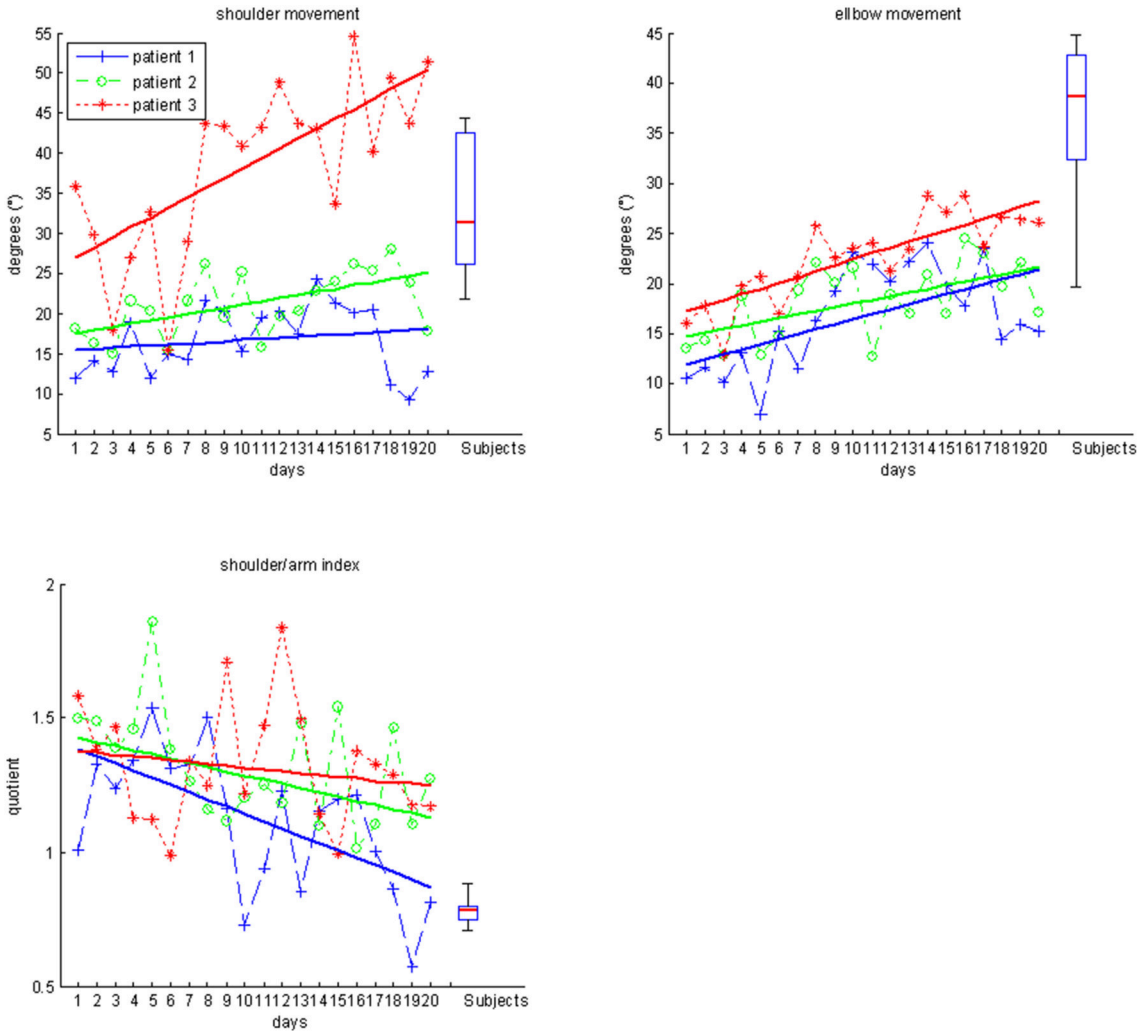

FIGURE 4 | Movement quality data for subjects (boxplots) and individual patients over the time course of training.

closed-loop interfaces follow an operant conditioning rationale, providing contingent feedback to facilitate self-regulation of specific brain activity which is considered to be beneficial for recovery and might ultimately lead to functional gains (Bauer and Gharabaghi, 2015a). Accordingly, these brain-robot interfaces were found to constitute a back-door to the motor system (Bauer et al., 2015; Gharabaghi et al., 2014a), since this type of feedback training may result in connectivity changes of cortico-spinal (Kraus et al., 2016a) and cortico-cortical motor networks (Vukelić et al., 2014; Vukelić and Gharabaghi, 2015a,b) and thereby lead to behavioral gains after the intervention (Naros et al., 2016b). Recently, pilot data has suggested that such restorative brain-robot interfaces may even lead to task-specific motor improvement in chronic stroke (Naros and Gharabaghi, 2015).

Problematic for restorative approaches is, however, that the considerable challenge of these devices (Bauer and Gharabaghi, 2015b; Fels et al., 2015) might condition the patients to explore alternative, i.e., therapeutically non-desired, strategies (Gharabaghi et al., 2014b). Particularly in patients with severe impairments, motor compensation could limit genuine motor restoration. In this context, detection and closed-loop feedback of movement quality during rehabilitation exercises would allow differentiating recovery from compensation and thus encourage the relearning of premorbid movement patterns. For those patients, however, who benefit less from the implicit closed-loop information provided in the presented set-up (e.g., patient 3) more explicit feedback or even segmental movement restriction by the orthosis might be necessary to reinforce the targeted movement pattern.

In conclusion, virtual reality visualization and feedback of joint-specific movement kinematics facilitates to monitor the evolution of upper extremity movement kinematics and to quantify the individual degree of natural movement restoration in the course of rehabilitation training of severely motor impaired patients; controlled studies with a larger cohort of stroke patients

need to investigate whether this approach also allows to achieve the rehabilitation goals in accordance with the individual capacity for functional recovery.

AUTHOR CONTRIBUTIONS

FG participated in the study design and software development, supervised the measurement sessions and carried the data analysis. GN supervised the measurement sessions. AG participated in the study design and data analysis. Authors jointly drafted and approved the final manuscript.

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Large-scale resting state network correlates of cognitive impairment in Parkinson's disease and related dopaminergic deficits

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Cognitive impairment is a common non-motor feature of Parkinson's disease (PD). Understanding the neural mechanisms of this deficit is crucial for the development of efficient methods for treatment monitoring and augmentation of cognitive functions in PD patients. The current study aimed to investigate resting state fMRI correlates of cognitive impairment in PD from a large-scale network perspective, and to assess the impact of dopamine deficiency on these networks. Thirty PD patients with resting state fMRI were included from the Parkinson's Progression Marker Initiative (PPMI) database. Eighteen patients from this sample were also scanned with ^{123}I-FP-CIT SPECT. A standardized neuropsychological battery was administered, evaluating verbal memory, visuospatial, and executive cognitive domains. Image preprocessing was performed using an SPM8-based workflow, obtaining time-series from 90 regions-of-interest (ROIs) defined from the AAL brain atlas. The Brain Connectivity Toolbox (BCT) was used to extract nodal strength from all ROIs, and modularity of the cognitive circuitry determined using the meta-analytical software Neurosynth. Brain-behavior covariance patterns between cognitive functions and nodal strength were estimated using Partial Least Squares. Extracted latent variable (LV) scores were matched with the performances in the three cognitive domains (memory, visuospatial, and executive) and striatal dopamine transporter binding ratios (SBR) using linear modeling. Finally, influence of nigrostriatal dopaminergic deficiency on the modularity of the "cognitive network" was analyzed. For the range of deficits studied, better executive performance was associated with increased dorsal fronto-parietal cortical processing and inhibited subcortical and primary sensory involvement. This profile was also characterized by a relative preservation of nigrostriatal dopaminergic function. The profile associated with better memory performance correlated with increased prefronto-limbic processing, and was not associated with presynaptic striatal dopamine uptake. SBR ratios were negatively correlated with modularity of the "cognitive network," suggesting integrative effects of the preserved nigrostriatal dopamine system on this circuitry.

Keywords: parkinson's disease, cognition, dopamine, resting state fMRI, SPECT, graph theory, nodal strength, modularity

INTRODUCTION

Cognitive impairment is a very important and common non-motor feature of Parkinson's disease (PD) with a major impact on patients' and caregivers' quality of life, as well as healthcare costs (Muslimovic et al., 2005; Vossius et al., 2011; Svenningsson et al., 2012). Approximately one-fifth of newly diagnosed PD patients fulfill clinical criteria for mild cognitive impairment (PD-MCI) (Aarsland et al., 2009) and about one-sixth develop dementia after 5 years (Williams-Gray et al., 2009).

Although the exact role and mechanisms of the dopaminergic system in cognition are still a matter of debate, there is no doubt that its preservation is crucial for cognitive functioning of PD patients. Thus, there is strong evidence suggesting that the impairment of at least 3 major dopaminergic pathways (nigrostriatal, mesocortical, mesolimbic) originating in the brainstem play a very important role in cognitive dysfunction associated with PD (Narayanan et al., 2013).

Previous neuroimaging studies assessing brain networks *in vivo* have shown impairment of the dopaminergic pathways and related neural circuits in PD. Numerous studies on cognitive dysfunction associated with PD have revealed structural and functional abnormalities within the

cortico-strio-thalamo-cortical circuits, known to be largely modulated by the dopaminergic system (Hirano et al., 2012; Christopher and Strafella, 2013).

Decreased 6-[^{18}F]-fluorodopa (^{18}F-DOPA) uptake in the anterior cingulate cortex, ventral striatum and right caudate nucleus has been found in PD patients with dementia (PDD) compared to PD (Ito et al., 2002). Studies employing Single Photon Emission Computed Tomography (SPECT) with the dopamine transporter-binding ligands (DaTSCAN) also suggest more severe striatal presynaptic dopaminergic deficiency in PDD compared to PD patients, especially in the caudate nuclei (O'Brien et al., 2004). In addition, there is also evidence suggesting an association between striatal ^{18}F-DOPA uptake and executive performance in PD patients (Bruck et al., 2001; Cheesman et al., 2005; Cropley et al., 2008).

Several ^{18}F-fludeoxyglucose Positron Emission Tomography (FDG-PET) studies analyzing brain networks in PD have identified partially overlapping patterns of brain metabolic changes associated with cognitive impairment in multiple domains, suggesting that the PD-related profile of cognitive impairment is associated with reduced glucose metabolism mainly in prefrontal, parietal, hippocampal, and striatal regions (Mentis et al., 2002; Huang et al., 2007a,b; Eidelberg, 2009). $H_2^{15}O$-PET studies have shown an impaired basal ganglia and dorsolateral prefrontal response during executive task performance in PD (Owen et al., 1998; Dagher et al., 2001; Cools et al., 2002).

Functional MRI studies have also revealed abnormalities within the frontal-subcortical circuits in patients with PD. For instance, an abnormal fronto-striatal response during executive task performance has been found in cognitively impaired PD patients compared to non-impaired ones (Lewis et al., 2003). Another fMRI study assessing working memory and motor functions in ON and OFF dopaminergic medication states in PD patients (Mattay et al., 2002) found increased prefrontal and parietal activations during the working memory task performance in the OFF state, which were positively correlated with errors during the task. Studies focusing on set-shifting paradigms have found a PD-associated pattern of prefrontal and parietal response characterized by either reduced or increased activation depending on whether the caudate nucleus was involved in the task (Monchi et al., 2004, 2007).

Notably, a pharmacological fMRI study in healthy subjects revealed a significant effect of L-dopa administration on striatal functional connectivity (Kelly et al., 2009). In addition to its effects on motor networks, L-dopa increased functional connectivity between the ventral striatum and ventrolateral prefrontal cortex, and disrupted connectivity of the striatum with components of the default mode network (Kelly et al., 2009). Impaired deactivation of the default mode network during executive task performance has been reported in several fMRI studies of PD (Tinaz et al., 2008; Van Eimeren et al., 2009). Resting state fMRI studies have reported abnormal cortico-striatal connectivity in PD (Wu et al., 2009; Helmich et al., 2010; Kwak et al., 2010), while L-DOPA administration has been shown to enhance functional connectivity in the frontal areas of the sensorimotor network (Esposito et al., 2013).

The brain is a complex biological system that demonstrates emergent network properties on different scales, even at a cellular and single-structure level (Welsh et al., 2010). At the cellular scale, neocortical neurons are organized into sets of structurally and physiologically merged modules (Mountcastle, 1997), which in turn, are grouped into functionally segregated hypercolumns, wired with inter-modular connections. At the larger scale, system-wide coordination of the brain networks give rise to the coherent dynamic states that support cognitive functions and behavior (Sporns, 2013). Large-scale network architecture of the human brain appears to combine two principles of structural and functional organization. On the one hand, densely connected network modules or communities promote specialized processing and *functional segregation*. On the other hand, these specialized communities are interconnected via long-distance pathways that ensure efficient *functional integration* across multiple functional domains. Maintaining the balance between segregation and integration is thought to be essential for establishing complex network dynamics that support cognition (Sporns, 2010).

Recent advances in neuroscience and mathematical modeling have made it possible to apply classical concepts of graph theory to the analysis of brain network structure and dynamics (Rubinov and Sporns, 2010; Sporns, 2010). Graph-theoretical studies of structural and functional networks of the brain have revealed "small-world" properties (Achard and Bullmore, 2007), i.e., the coexistence of dense local connectivity with relatively sparse long-range connections. Such small-world networks combine high clustering with a relatively short path length between any pair of the elements (e.g., brain regions). The "small-world" model may be of functional importance as it balances functional segregation (high modularity or clustering) and functional integration (short path length) and thus offers a network architecture that may be well-suited for neuronal information processing (Sporns and Zwi, 2004).

To date, there are very few studies of PD employing graph theoretical framework for fMRI data analysis. Skidmore et al. found reduced whole-brain global efficiency in PD (Skidmore et al., 2011). Compared to healthy controls, 14 PD patients included in the study demonstrated reduced local efficiency (nodal level) in the precentral regions, primary and secondary visual cortex. Another recent study found global reduction of network-level processing efficacy in PD. Analysis of network modules indicated decreased interaction of the visual network with other brain modules, but abnormally increased connectivity within the sensorimotor network. The authors interpreted the latter as a compensatory mechanism aimed at overcoming the striato-cortical functional deficit within the motor loops, which may also be associated with loss of mutual inhibition between brain networks (Gottlich et al., 2013).

To the best of our knowledge, there are no previous studies assessing brain correlates of PD-related cognitive impairment employing both dopamine transporter imaging and fMRI with graph theory metrics.

In the present study, we assessed global and local network-level correlates of cognitive dysfunction and related dopaminergic impairment in PD using the graph theory metrics of nodal strength and modularity.

We hypothesized that the PD-related profile of cognitive impairment would be associated mainly with abnormalities within the fronto-subcortical (impaired cortico-striatal connectivity) and fronto-parietal circuits, which are closely related to nigrostriatal deficiency.

METHODS

The main workflow steps are illustrated in **Figure S1**.

INCLUSION AND EXCLUSION CRITERIA

We included all 30 subjects (31 minus one subject excluded during quality control due to "cuts" of dorsal cortical areas) with rs-fMRI enrolled in the Parkinson's Progression Marker Initiative (PPMI) (in total 452 PD patients), a multicenter study launched in 2010 designed to identify progression biomarkers in newly diagnosed PD patients (www.ppmi-info.org/data).

Inclusion criteria required that subjects must have at least two of the following symptoms: resting tremor, bradykinesia, rigidity or either asymmetric resting tremor or asymmetric bradykinesia. In addition, the subjects had to be drug naïve, Hoehn and Yahr stage I or II at baseline, and a screening ^{123}I-FP-CIT SPECT scan, sensitive to the loss of striatal dopamine transporter (DaT) binding.

Exclusion criteria were atypical PD syndromes due to drugs or metabolic disorders, encephalitis, or other degenerative diseases. In addition, it was required that the subject was not taking levodopa, DA agonists, MAO-B inhibitors, amantadine, or other PD medication; or had taken levodopa or dopamine agonists prior to baseline for more than a total of 60 days.

NEUROPSYCHOLOGICAL ASSESSMENT

In addition to a cognitive screening test, the Montreal Cognitive Assessment (MoCA), all subjects underwent a neuropsychological test battery developed to assess major cognitive domains affected by PD.

Visuospatial function was evaluated using the 15-item version of the Benton's Judgment of Line Orientation Test, which examines the ability of a subject to estimate angular relationships between line segments by visually matching angled line pairs to 11 numbered radii forming a semi-circle (Benton et al., 1978).

Verbal memory was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) (Shapiro et al., 1999), which consists of presenting a list of 12 words over three learning trials. With each repetition, subjects are expected to learn additional words on the list and increase their performance with each trial. Total immediate recall or encoding (sum of trial 1–3) and delayed recall (after 20–25 min) scores were included in this study.

Executive functions were evaluated using three semantic fluency tests (names of animals, fruits, and vegetables, in 1 min each), the MoCA subtests of phonemic fluency (words that start from the letter "F," in 1 min) and alternating trail making (drawing a line, going from a number to a letter, in ascending order; score 0–1).

Attention was assessed by the Letter-Number Sequencing Test (LNST), in which a combination of numbers and letters is read to the subject who is then asked to recall the numbers, first in ascending order and then the letters in alphabetical order. The Symbol Digit Modalities Test (SDMT) was also used to assess attention, in which specific numbers had to be paired with geometric figures based on a reference key within 90 s.

COGNITIVE DOMAINS

Three cognitive domains were calculated based on the standardized tests for memory, visuospatial, and attention/executive functioning. Raw values were converted to z-scores using the mean and standard deviation of the healthy control group. Domain composite scores were calculated by averaging z-scores of the standardized tests in each cognitive domain.

In the *memory domain*, three learning trials and the delayed recall of HVLT-R were included. The *visuospatial domain* included the Benton judgment of line orientation. The *attention/executive domain* included the LNST, SDMT, semantic fluency, and the phonemic fluency test. No corrections were performed to adjust the tests scores for age or gender given that the subsequent analyses included these variables as nuisances.

Since the calculated composite scores for cognitive domains were scaled and reflected positive cognitive performance (the higher the score, the better functioning in a corresponding domain), we defined the "motor" domain by inverting and scaling UPDRS-III raw scores in order to achieve the same variable scale and direction (higher scores correspond to better motor function) when assessing and plotting the results.

AUTOMATED META-ANALYSIS IN NEUROSYNTH

In order to support our hypotheses and to objectively identify regions that are relevant for cognitive functions, an automated search using the meta-analytical software Neurosynth (http://neurosynth.org) was undertaken. This approach utilizes text-mining and machine-learning techniques to perform probabilistic mapping between neural and cognitive states (Yarkoni et al., 2011). In the present study, the Python-based version (https://github.com/neurosynth/neurosynth) was used. The database was accessed on 24.10.13, searching for the key-words "executive" (237 studies), "visuospatial" ($n = 116$) and "memory" ($n = 1470$).

After the search overlapping patterns were found between cognitive domains. They were in line with the regions that have revealed an association with cognitive impairment in PD highlighted in the introduction. Thus, the profile of visuospatial functions included prefrontal, parietal, and occipital regions. The "executive" pattern contained prefrontal [with more extended involvement of dorsolateral prefrontal cortex (DLPFC)], cingulate, superior parietal, temporo-occipital, basal ganglia, and cerebellar regions. Finally, the "memory" profile, in addition to prefrontal and parietal regions, also included hippocampus, temporal areas, and basal ganglia.

Due to the observed overlap, the resulting statistical maps were merged and overlaid with the Automated Anatomical Labeling (AAL) atlas in order to have an unbiased definition of ROIs associated with cognitive functions for further network analysis. The main steps of the meta-analysis and the resulting maps are illustrated in **Figure S2**.

MRI

Image acquisition

A standardized MRI protocol included acquisition of whole-brain structural and functional scans on 3 Tesla Siemens Trio Tim MR system. More details can be found in the MRI technical operations manual at http://www.ppmi-info.org/.

3D T1 structural images were acquired in a sagittal orientation using a MPRAGE GRAPPA protocol with Repetition Time (TR) = 2300 ms, Echo Time (TE) = 2.98 ms, Field of View (FoV) = 256 mm, Flip Angle (FA) = 9° and 1 mm^3 isotropic voxel.

For each subject, 212 BOLD echo-planar rs-fMRI images (40 slices each, ascending direction) were acquired during a 8 min, 29 s scanning session (acquisition parameters: TR = 2400 ms, TE = 25 ms, FoV = 222 mm, FA = 80° and 3.3 mm^3 isotropic voxels). Subjects were instructed to rest quietly, keeping their eyes open and not to fall asleep.

^{123}I-FP-CIT SPECT

In the fMRI + DaTSCAN subgroup (n = 18), only those PD patients who had both fMRI and DaTSCAN acquired within less than a week interval were included.

Image acquisition was performed 4 ± 0.5 h after injection of ^{123}I-FP-CIT, a time-point at which striatal specific binding ratios are stable (Booij et al., 1999) with a target dose of 185 MBq. The radiopharmaceutical was provided as a unit dose and filled to a standard volume, which was re-assayed.

Raw projection data were acquired into a 128 × 128 matrix with steps of 3 or 4 degrees for the total projections. Image preprocessing (reconstruction, attenuation correction, spatial normalization) was performed using the Hermes software (Medical Solutions, Stockholm, Sweden) at a central SPECT Core lab in New Haven (Connecticut, United States). Specific binding ratios were calculated for the left and right caudate nuclei according to specific binding ratio = (L/R Caudate)/(Occipital area) − 1 and then averaged for further analysis.

IMAGE PREPROCESSING

As a first step, a population template was generated from the bias-corrected T1 structural images using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007) in order to improve normalization quality.

For the fMRI data, two initial echo-planar volumes were automatically removed by the scanner software to minimize T1 effects on the T2* echo-planar images, and the remaining 210 volumes underwent preprocessing in the SPM8-based (http://www.fil.ion.ucl.ac.uk/spm) pipeline implemented in the Data Processing Assistant for Resting-State fMRI: Advanced Edition (DPARSFA, version 2.3) (Chao-Gan and Yu-Feng, 2010), installed within the MATLAB environment (Matlab 8.0 and Statistics Toolbox, 2012).

Next, functional images underwent the following preprocessing steps: spatial realignment and slice-timing correction, co-registration with the high-resolution structural scans. Finally, the co-registered BOLD volumes were normalized into standardized Montreal Neurological Institute (MNI) space using the DARTEL template and resampled to 3 mm^3 isotropic voxels. Spurious variance was reduced by a voxel-specific head motion correction (Satterthwaite et al., 2013) and by regressing-out time-series from the white matter and cerebrospinal fluid. Next, the images were band-pass filtered to eliminate biologically non-relevant signals (Biswal et al., 1995; Lowe et al., 1998) (it was not necessary to use large smoothing kernels due to a ROI-based framework implemented in the study), and the resulting low-frequency fluctuations were extracted from 90 regions-of-interest (ROIs) defined in the AAL atlas (Tzourio-Mazoyer et al., 2002) and were used in the subsequent network analysis (Rubinov and Sporns, 2010).

DATA ANALYSIS

Network analysis

The data analysis workflow was developed in order to assess both regional and global network-level correlates of presynaptic DAT uptake and cognitive functions. To do this, two metrics were selected: *nodal strength* (local measure) and *modularity* of a network (global measure).

Generalization of nodal strength and modularity for positive and negative connections

In binarized networks, the number of edges emanating from a particular node is known as its degree. For non-binarized networks, this metric has generalization called nodal strength (weighted degree), defined as the sum of neighboring link weights (Rubinov and Sporns, 2010).

Although the source of negative correlations in rs-fMRI is still a matter of debate (Fox et al., 2009; Murphy et al., 2009), there is strong evidence supporting a biological origin (Chang and Glover, 2009). In light of this, generalizations of several weighted graph theory metrics have been developed taking into account negative correlations (Rubinov and Sporns, 2011).

Thus, nodal strength can be calculated for positive and negative connections. The corresponding definition is straightforward:

$$S_i^{\pm} = \sum_{j \in N} w_{ij}^{\pm} \quad (1)$$

[Equation (1), adopted from Rubinov and Sporns, 2011] Where:

N—set of all nodes in the network;

(i, j)—link between nodes i and j ($i, j \in N$), associated with connection weights w_{ij} ($0 < |w| < 1$)

Nodal strength can therefore be computed for both positive and negative weights (±). In our analysis, the total strength of both positive and negative weights was used.

A widely used metric for network modularity is formally defined as the fraction of the edges that are within a given set of communities minus the expected fraction of edges if the network was randomly wired (Newman, 2006). The metric therefore serves as a global large-scale network measure that allows quantification of the community structure of the brain. Higher modularity values for a particular network are generally associated with denser within-modular connections, but sparser connections between nodes that are in different modules.

Generalization of the modularity to both positive and negative correlations is more complex than nodal strength due to the differences in significance of positive and negative weights when

determining modularity-partitions. Therefore, a non-symmetric generalization of network modularity has been proposed as:

$$Q^* = Q^+ + \frac{v^-}{v^+ + v^-} Q^- \quad (2a)$$

or more complete definition:

$$Q^* = \frac{1}{v^+} \sum_{ij} \left(w_{ij}^+ - e_{ij}^+ \right) \delta_{M_i M_j} - \frac{v^-}{v^+ + v^-} \sum_{ij} \left(w_{ij}^- - e_{ij}^- \right) \delta_{M_i M_j} \quad (2b)$$

Both equations are adopted from Rubinov and Sporns (2011)

Where:

$Q^{\pm}$—modularity;

$\left(w_{ij}^{\pm} - e_{ij}^{\pm} \right)$—difference between present within-module connection weights w and chance-expected within-module connection weights e;

$\delta_{M_i M_j} = 1$, when i and j are in the same module and $\delta_{M_i M_j} = 0$ otherwise.

$v^{\pm} = \sum_{i \in N} s_i^{\pm}$—total weight (the sum of all positive or negative weights)

The Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net) (Rubinov and Sporns, 2010) was used to compute the described measures. Of note, connectivity matrices were neither thresholded nor binarized. Instead we employed a strategy that aimed to analyze weighted graphs by taking into account both positive and negative weights.

Next, the analysis proceeded in two directions with the aim of assessing local and global network-level correlates of cognitive functioning in PD and the impact of nigrostriatal dopaminergic deficiency on these networks.

All statistical analyses were performed using the R programming language, version 3.0.1 (R Core Team, 2013).

Dimensionality reduction: covariance patterns between nodal strength and cognitive functions

Partial Least Squares Regression (PLSR) was performed to reduce the dimensionality of the data, estimating latent components associated with composite scores for each domain (executive, memory, visuospatial).

PLSR is an effective data-driven method that allows high-dimensional associations between explanatory and response variables to be reduced into a small set of latent variables (LVs) (Wold et al., 1984). After decomposition, each of the LVs represents a distinct pattern of brain–behavior associations.

The following elements of these components were of particular interest in our study: (1) eigenvector (loadings) showing the degree to which a given LV contributes to the variance within the X-matrix (in our case, brain network measures), and (2) a set of scores representing a transform of a particular data-point into a latent component's space (the degree to which a given component is "represented" in a particular subject).

The models were assessed with leave-one-out cross-validation. As a result, 3 LVs minimizing total Root Mean Squared Error Prediction (RMSEP) for all 3 domains were selected. For details, see **Figure S3**. Individual LV scores were subsequently correlated with 3 cognitive domains using motor function, age, and sex as nuisance covariates.

GLM formula:

$$\begin{aligned} \mathrm{LV_N}-\mathrm{score} \sim\ & (\text{executive domain}) + (\text{memory domain}) \\ & + (\text{visuospatial domain}) + (\text{motor domain}) \\ & + (\text{age}) + (\text{sex}). \end{aligned} \quad (3)$$

Finally, the scores were correlated with mean caudate DaT binding ratios in order to investigate which of them were influenced by nigrostriatal dopamine deficiency. The analysis was focused only on the caudate nuclei (without putamen), as this striatal structure is well-documented to be involved in cognition.

Due to the concerns regarding potential influence of motion artifacts, in addition to a voxel-specific correction strategy (Satterthwaite et al., 2013), analysis of motion with respect to the variables of interest (cognitive, motor domains, and age) was also performed. For this purpose, first principal component extracted from the absolute mean displacement values (x, y, and z axes) as well as relative displacements were used.

None of our variables of interest (executive, memory, and visuospatial domains) demonstrated significant association. The only significant associations were found for the motor domain ($p_{\text{mean displacement}} = 0.036$; $p_{\text{relative displacement}} = 0.035$) and age ($p_{\text{mean displacement}} = 0.026$), as expected. These variables were included in the modes as nuisance covariates.

Impact of nigrostriatal deficiency on the modularity of cognitive brain circuitry

For the second part, adjacency matrices were constructed using 60 AAL ROIs identified during the meta-analysis step (see Meta-Analysis section and **Figure S2**). Next, modularity was estimated based on both negative and positive weights [as described in Equations 2a and 2b].

Finally, an association between network modularity and mean DaT uptake in the caudate nuclei was analyzed using linear modeling.

RESULTS

DEMOGRAPHICS AND CLINICAL DATA

Demographics and clinical characteristics are shown in **Table 1**.

The data were representative of the entire DaTSCAN cohort of PD patients (results not shown). Of note, visuospatial functions were relatively less affected than executive and memory domains.

GRAPH THEORETICAL ANALYSIS

Brain-behavior covariance patterns

The analysis was performed with PLS LV-scores determined after the dimensionality reduction step (see corresponding Methods section).

Nodal strength

The first PLS LV captured global effects. Its higher scores were associated with higher strength of all 90 nodes with largest effects on motor, prefrontal cortices, and striatum. On a behavioral level,

Table 1 | Demographics and clinical data.

	Complete sample ($n = 30$)		Subsample* ($n = 18$)	
	Mean [±SD]	Median (range)	Mean [±SD]	Median (range)
Age	61.67 [±9.46]	62 (40–75)	60.11 [±9.04]	61 (44–75)
MoCA	26.67 [±3]	27 (15–30)	26.72 [±3.5]	27 (15–30)
ExecDom	−0.254 [±0.73]	−0.125 (−1.37–1.26)	−0.297 [±0.67]	−0.125 (−1.35–0.99)
MemDom	−0.51 [±1.2]	−0.41 (−2.81–1.47)	−0.73 [±1.26]	−0.51 (−2.81–1.25)
VspDom	0.06 [±0.78]	−0.06 (−1.57–0.95)	0.08 [±0.84]	0.44 (−1.57–0.95)
UPDRS III	20.2 [±10.6]	17 (7–47)	19.83 [±10.9]	17 (7–47)

Male/Female ratio was 2:1.

**Subsample of subjects who had both fMRI and DaTSCAN acquired within less than a week interval.*

MoCA, the Montreal Cognitive Assessment; ExecDom, "Executive" domain; MemDom, "Memory" domain; VspDom, "Visuospatial" domain; UPDRS III, part III of the Unified Parkinson's Disease Rating Scale.

Table 2 | Associations between component scores and behavioral data: nodal strength.

	Executive			Memory			Visuospatial			Motor		
	T	DOF	*p*	*T*	DOF	*p*	*T*	DOF	*p*	*T*	DOF	*p*
LV I	0.782	29	0.442	1.35	29	0.19	−0.89	29	0.383	3	29	0.006
LV II	−0.656	29	0.518	−2.45	29	0.022	−1.74	29	0.094	1.327	29	0.127
LV III	3.21	29	0.004	−1.74	29	0.096	1.65	29	0.113	−2.02	29	0.055

The table shows associations between latent variable (LV) scores extracted from the nodal strength data and performance in 3 cognitive (executive, memory, visuospatial) and motor domains. Positive significant associations are depicted in red and negative ones in blue.

In total, 3 models were fitted with component scores as dependent variables, cognitive domains as independent variables (other covariates: motor domain score [also shown here as an important confounder], age and sex).

***T**, t-statistics; **DOF**, degrees of freedom.*

this component was positively associated with motor function (see **Table 2**, **Figure 1**).

The second LV was associated with higher degree of posterior (supramarginal, superior parietal, posterior cingulate, occipital regions) and striatal nodes, and lower prefronto-limbic (orbitofrontal, anterior cingulate, parahippocampal, temporopolar regions) nodal strength (except for operculo-triangular, middle frontal areas, and left hippocampus, which demonstrated positive associations). Behaviorally, this component displayed a negative association with memory function, that is to say that better memory performance was associated with reversed component pattern, favoring the involvement of prefronto-limbic nodes (see **Table 2**, **Figure 1**).

The third LV, in turn, favored cortical-subcortical segregation with positive associations found in dorsal cortical nodes (dorsolateral prefrontal, frontal and parietal areas) and negative in subcortical structures (hippocampi, striatum, globus pallidus), primary visual, middle temporal, and paralimbic (ventral prefrontal) areas. Higher scores of this component were associated with better executive performance (see **Table 2**, **Figure 1**).

Latent variable scores and caudate DaT uptake

Analysis of the effects of nigrostriatal dopaminergic deficiency on the LVs estimated from the nodal strength revealed significant positive associations of mean caudate SBR ratios with I and III LV-scores (See **Table 3**, **Figure 2**).

This means that higher caudate DaT binding is associated with global increase of nodal strength and segregation toward more active dorsal cortical processing when the subject is at rest.

Modularity of the cognitive circuitry and caudate DaT binding

The analysis revealed negative effects of the preserved dopaminergic function on modularity of the cognitive circuit ($T = -3.6$, 17 DOF, $p = 0.002$), suggesting greater integration among regions within this network (see **Figure 3**).

DISCUSSION

To the best of our knowledge, this is the first study to assess large-scale network correlates of PD-related cognitive impairment and presynaptic dopaminergic deficiency, combining rs-fMRI and DaTSCAN. Higher executive functional scores were associated with higher nodal strength of dorsal cortical nodes (predominantly in dorsolateral prefrontal, premotor, and superior parietal regions) and lower involvement of subcortical, occipital, temporal, and ventral cortical nodes, suggesting that relative preservation of executive functions in PD is linked to the dominance of dorsal cortical processing with inhibition of subcortical, paralimbic, and primary sensory circuitry when the subject is at resting state with eyes open. This pattern was positively influenced by higher nigrostriatal dopaminergic function.

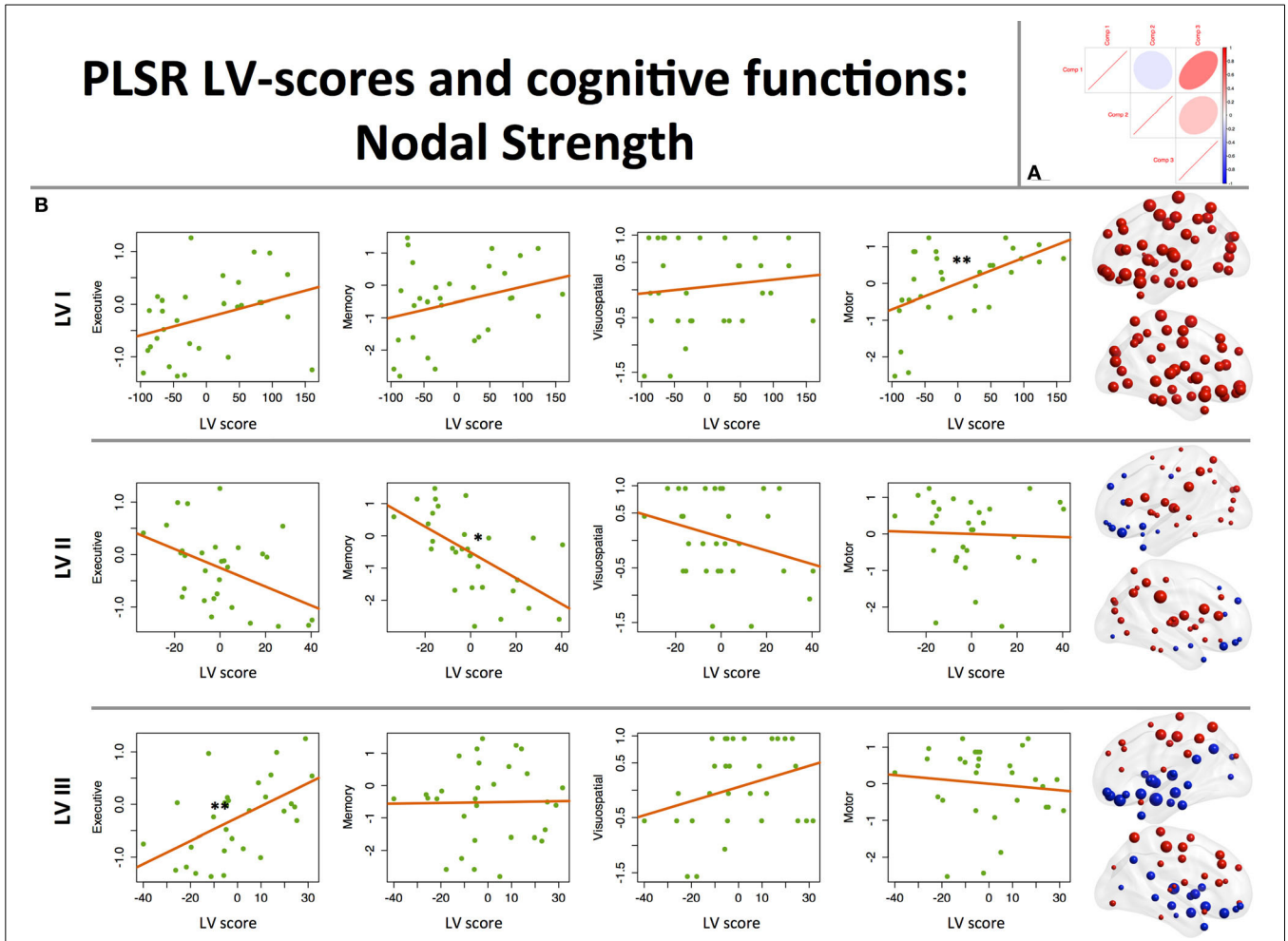

FIGURE 1 | Associations between component scores and behavioral data: nodal strength. (A) Between-component correlation plot. Positive association ($r = 0.5$) was found between latent variables (LVs) I and III. **(B)** Associations between LV scores extracted from the nodal strength data and performance in 3 cognitive (executive, memory, visuospatial) and motor domains. On the right-hand side of the graph, corresponding loading maps are depicted in brain space, reflecting the relevance of the nodes (spheres) for a particular LV, the magnitude of which is represented by nodal size. Positive loading values are depicted as red spheres, whereas negative ones are shown in blue. $^{*}p < 0.05$, $^{**}p < 0.01$.

Our results are consistent with an abnormally increased fronto-striatal connectivity found in a single-blind placebo-controlled rs-fMRI study of PD patients (Kwak et al., 2010), in which this hyperconnectivity was down-regulated by L-DOPA administration. Further analysis in this study revealed PD-related increase of power in the low-frequency band (0.02–0.05 Hz) in the striatum, which was also reduced after L-DOPA administration. Of note, this reduction correlated with L-DOPA-associated cognitive improvement. Apart from this, an increase in spontaneous oscillatory activity in the 10–35 Hz range (beta frequency band), occurring within the basal ganglia-thalamocortical networks and suppressed by dopaminergic treatment, is a well-replicated pathophysiological finding in PD (Brown et al., 2001; Levy et al., 2002; Gatev et al., 2006; Hammond et al., 2007), which provides additional support of our results converging from other imaging modalities.

The pattern associated with higher scores in the memory domain favoring prefronto-limbic processing did not reveal associations with presynaptic striatal dopamine uptake in the present study. The latter suggests that other mechanisms may be involved in the development of memory impairment associated with PD. The most likely ones are mesocortical dopaminergic deficiency (Narayanan et al., 2013) and impaired cortical cholinergic function (Bohnen et al., 2003), which in turn may at least be partly associated with concomitant cortical atrophy (Weintraub et al., 2012).

Of note, our study did not find any correlates of visuospatial impairment. However, this finding may be influenced by small sample size and due to the fact that visuospatial function was only mildly affected in the present cohort.

According to Mink's hypothesis (Mink, 1996), the basal ganglia play a crucial role in sustaining the balance between facilitation and suppression of movements. If we consider executive functions as the "movement of thoughts" a similar analogy can be drawn within this context. Indeed, cognitive frontal-subcortical loops is a widely accepted notion, where the DLPFC circuit has been

documented to mediate set-shifting, complex problem-solving, retrieval abilities, organizational strategies, concept-formation, working memory (Zgaljardic et al., 2006), and other executive functions that are known to be affected in PD. Preserved nigrostriatal dopamine function therefore not only allows effective execution and termination of motor activity, but may also implement smooth switching between cognitive patterns, controlling mutual inhibition and/or facilitation of fronto-subcortical circuits. This is also supported by computational models of the basal ganglia that highlight their routing role in various cognitive functions, such as for example action-selection (Stocco et al., 2010).

Table 3 | Latent variable scores and mean caudate DaT binding.

	CN DaT binding		
	T	**DOF**	***p***
LV I	2.87	17	0.011
LV II	−0.096	17	0.925
LV III	2.281	17	0.037

The table shows associations of the PLS latent variables (LVs) extracted during the dimensionality reduction step with nigrostriatal dopaminergic function measured by ^{123}I-FP-CIT SPECT (mean caudate SBR ratios). Positive significant associations (depicted in red) were found for LVs I ("global/motor") and III ("executive").

*CN, Caudate Nucleus; DaT, Dopamine Transporter; **T**, t-statistics; **DOF**, degrees of freedom.*

In general, higher DaT binding values were associated with global integrative effects on the brain (global increase of nodal strength). This was also confirmed for the cognitive circuitry (defined during meta-analysis), where higher DaT SBR ratios (relative preservation of dopaminergic function) were associated with lower network-level modularity, suggesting that dopamine favors integration of the cognitive network when the subject is at rest. These results are in line with previous fMRI studies that indicated globally impaired network-level processing in PD (Skidmore et al., 2011; Gottlich et al., 2013). Negative effects of the preserved dopaminergic function on the modularity of cognitive circuitry are also in line with previous literature. Thus, a recent randomized double-blind rs-fMRI study of healthy subjects with bromocriptine administration (dopamine agonist) revealed drug-induced decreases in modularity, estimated for the whole brain (White et al., 2013). Our results also suggest that preserved nigrostriatal dopaminergic system allows supporting integrity of the cognitive network when a subject is at rest. In

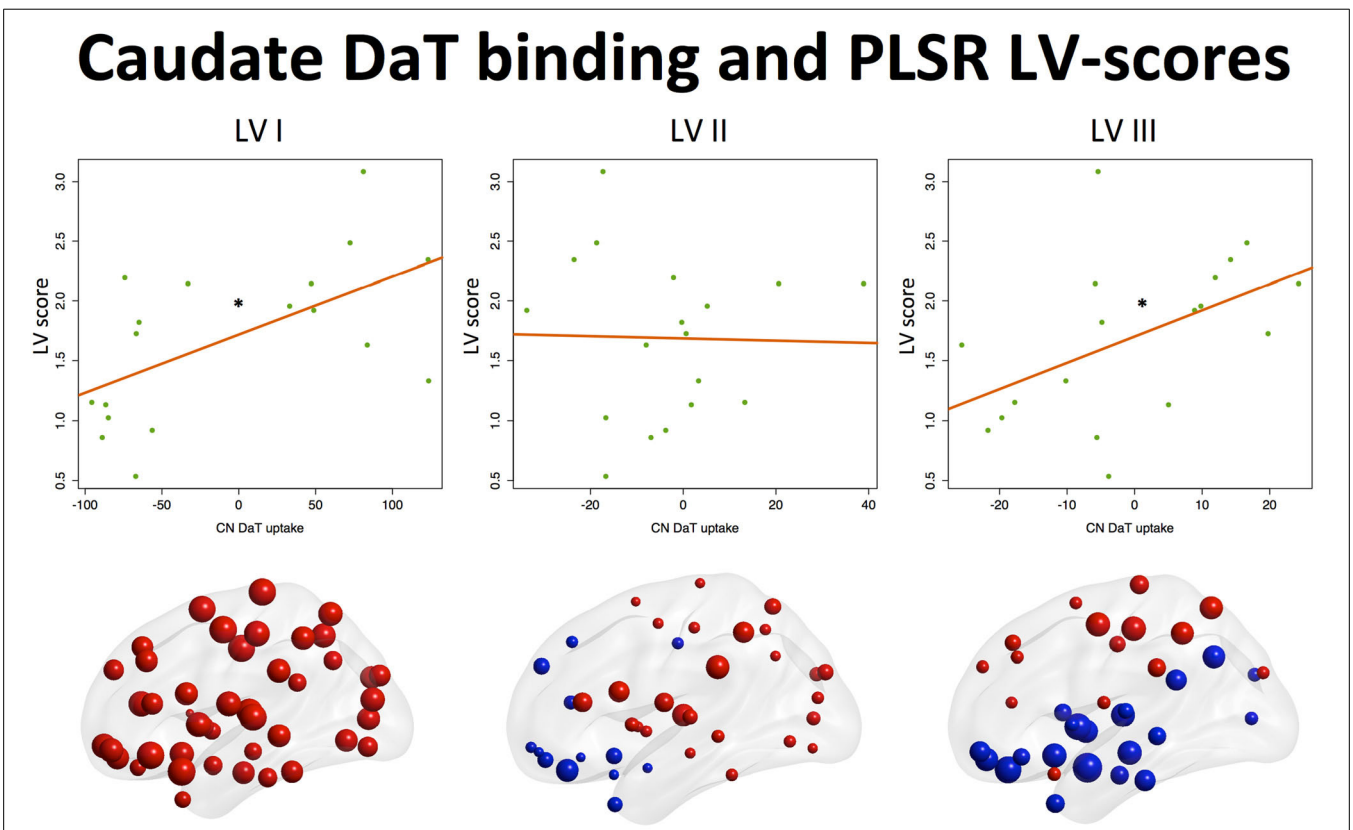

FIGURE 2 | Associations between component scores and mean caudate DaT binding. Associations of latent variable (LV) scores extracted from the nodal strength data with nigrostriatal dopaminergic function measured by ^{123}I-FP-CIT SPECT (mean caudate SBR ratios). Positive associations ($*p < 0.05$) were found for the Ist ("global/motor") and IIIrd ("executive") LVs. Corresponding loading maps are depicted in brain space, reflecting the relevance of the nodes (spheres) for a particular LV, the magnitude of which is represented by nodal size. Positive loading values are depicted as red spheres, whereas negative ones are shown in blue.

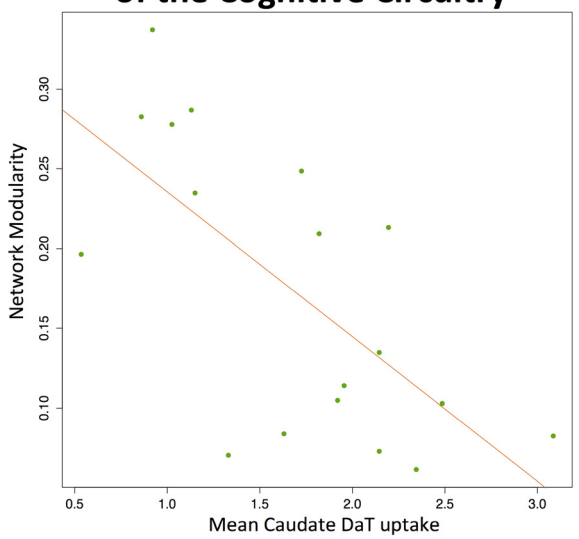

FIGURE 3 | Caudate DaT uptake and modularity of the cognitive circuitry at rest. The figure shows significant ($p < 0.01$) negative association between modularity of the cognitive circuitry (identified with automated meta-analysis) and nigrostriatal dopaminergic function measured by ^{123}I-FP-CIT SPECT (mean caudate SBR ratios).

the light of this, it would be interesting to assess the dynamics of cognitive circuitry during performance of particular executive tasks or multi-tasking, where dopamine may have different or even opposite effects on network modularity. This is supported by previous functional imaging studies of executive functions in PD, revealing that hypodopaminergic states are associated with increased prefrontal cortical responses during performance of corresponding tasks (Mattay et al., 2002), whereas L-dopa administration, in contrast, decreases it (Cools et al., 2002). In this context, it is also worth mentioning an event-related fMRI study that found PD-related brain abnormalities during performance of the set-shifting task specifically developed to elicit caudate responses (Monchi et al., 2007). Compared to the control group, patients demonstrated increased cortical activation in the condition not specifically requiring the caudate nucleus, whereas decreased cortical activation was observed in the task that involved the caudate nucleus. These studies, however, are not focused on any specific dopaminergic system, looking at general dopamine-related effects instead, and therefore do not necessarily confirm the role of exactly nigrostriatal dopaminergic system in these phenomena.

Finally, a recently published graph theoretical MEG study with longitudinal design found that progression of PD is associated with growing impairment of local integration (measured by clustering coefficient) in multiple frequency bands and loss of global brain network efficiency (based on path length) in the alpha2 frequency band. This deterioration was, in turn, correlated with cognitive and motor impairment observed during disease progression (Olde Dubbelink et al., 2014). These findings provide additional support for our results, also suggesting global positive effects of dopaminergic preservation on efficient functioning of the brain networks.

The main limitation of the present study is a relatively small sample size. In addition, the cross-sectional design complicates causal interpretation of the results. Apart from this, the resting state setting itself hampers direct interpretation of the findings with regard to the role of brain networks in cognitive task performance. Active cognitive processing is likely associated with patterns of brain dynamics that are different compared to the ones occurring when the subject is at rest. These patterns in turn may have different associations with altered dopaminergic function in PD. Therefore, this presents a need for further studies of brain dynamics underlying cognitive processing in PD and related dopaminergic deficits.

The main strengths are a multimodal approach and graph theoretical setting that have not yet been implemented together for clarifying brain mechanisms of PD-related cognitive impairment. Further strengths are a relatively broad cognitive evaluation combining multiple tests to assess three major functional domains and the drug-naïve status of the participants. Of note, although the present study specifically investigated the nigrostriatal system, the deficiency measured by ^{123}I-FP-CIT SPECT might also reflect indirect effects of neurodegeneration of dopaminergic neurons within other pathways, since the severity of dopaminergic deficits may correlate across different systems. Therefore, the results should be interpreted with caution.

To summarize, our study found that PD-related executive impairment is associated with altered balance between cortical and subcortical processing at rest, when contribution of the dorsal cortex is getting abnormally suppressed, and subcortical processing is disinhibited. This pattern (unlike brain profiles of visuospatial and memory impairment) is linked to nigrostriatal deficiency, which also has disruptive effects on cognitive circuitry at the network scale.

The results provide evidence for the contribution of the nigrostrital dopaminergic system in human cognition, and the described concept can potentially be utilized in future interventional studies to monitor the effects of treatments, including the approaches that augment cognitive functions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnsys.2014.00045/abstract

Figure S1 | Study Workflow. The study workflow consisted of IV main steps: (I) Selection of 30 PD subjects with fMRI data from the complete PPMI cohort and an fMRI + DaTSCAN subsample of 18 subjects; (II) Preparation of the data for further analysis that, in turn, included (IIa) calculation of composite scores for 3 cognitive domains, (IIb) automated meta-analysis to define "cognitive network," (IIc) image preprocessing and network measure extraction; (III) Dimensionality reduction with PLS followed by parametric tests evaluating associations between latent variable (LV) scores and cognitive functions; (IV) Final analysis assessing influence of caudate dopamine transporter (DaT) uptake on LV scores and modularity of the "cognitive network.

Figure S2 | Automated meta-analysis workflow. An automated search using the meta-analytical software Neurosynth (http://neurosynth.org) was undertaken in order to identify regions that are relevant for cognitive functions. The key-words "executive" (237 studies), "visuospatial" ($n = 116$) and "memory" ($n = 1470$). The profile of visuospatial functions included prefrontal, parietal, and occipital regions. The "executive" pattern contained prefrontal (with more extended involvement of DLPFC), cingulate, superior parietal, temporo-occipital, basal ganglia, and cerebellar regions. Finally, the "memory" profile, in addition to prefrontal and parietal regions, also included hippocampus, temporal areas, and basal ganglia. Due to the observed overlap, the resulting statistical maps were merged and overlaid with the Automated Anatomical Labeling (AAL) atlas defining cognitive circuitry, the modularity of which was then correlated with nigrostriatal function measured by ^{123}I-FP-CIT Single-Photon Emission Computed Tomography.

Figure S3 | Latent variable selection. The figure shows Root Mean Squared Error Prediction (RMSEP) as a function of a number of PLS latent variables (LVs). The maximum number of LVs was selected that minimized total training (red dashed line) and leave-one-out cross-validation (green solid line) errors for all the domains ($n = 3$).

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Multifaceted effects of noisy galvanic vestibular stimulation on manual tracking behavior in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative movement disorder that is characterized clinically by slowness of movement, rigidity, tremor, postural instability, and often cognitive impairments. Recent studies have demonstrated altered cortico-basal ganglia rhythms in PD, which raises the possibility of a role for non-invasive stimulation therapies such as noisy galvanic vestibular stimulation (GVS). We applied noisy GVS to 12 mild-moderately affected PD subjects (Hoehn and Yahr 1.5–2.5) off medication while they performed a sinusoidal visuomotor joystick tracking task, which alternated between 2 task conditions depending on whether the displayed cursor position underestimated the actual error by 30% ('Better') or overestimated by 200% ('Worse'). Either sham or subthreshold, noisy GVS (0.1–10 Hz, 1/f-type power spectrum) was applied in pseudorandom order. We used exploratory (linear discriminant analysis with bootstrapping) and confirmatory (robust multivariate linear regression) methods to determine if the presence of GVS significantly affected our ability to predict cursor position based on target variables. Variables related to displayed error were robustly seen to discriminate GVS in all subjects particularly in the Worse condition. If we considered higher frequency components of the cursor trajectory as "noise," the signal-to-noise ratio of cursor trajectory was significantly increased during the GVS stimulation. The results suggest that noisy GVS influenced motor performance of the PD subjects, and we speculate that they were elicited through a combination of mechanisms: enhanced cingulate activity resulting in modulation of frontal midline theta rhythms, improved signal processing in neuromotor system via stochastic facilitation and/or enhanced "vigor" known to be deficient in PD subjects. Further work is required to determine if GVS has a selective effect on corrective submovements that could not be detected by the current analyses.

Keywords: Parkinson's disease, vestibular system, GVS, manual tracking, discriminant analysis

INTRODUCTION

Motor symptoms in Parkinson's disease (PD) characteristically manifest themselves as tremor, rigidity, akinesia/bradykinesia and postural instability. While levodopa is the gold standard treatment for PD, chronic use eventually leads to the long-term development of side effects, such as motor fluctuations, dyskinesias, and psychiatric disorders (Pontone et al., 2006; Weintraub et al., 2006). Surgical treatments, including deep brain stimulation targeted to subcortical nuclei, have provided effective therapeutic benefits, but are complex and invasive (Okun, 2012). With recent technological advances, numerous novel stimulatory techniques for PD treatment are presently being explored (Fuentes et al., 2009; Thevathasan et al., 2010; Samoudi et al., 2012; Faught and Tatum, 2013). Non-invasive brain stimulation techniques are currently a growing avenue of interest for PD and other neurological disorders due to their safety, tolerability and minimally invasive nature (Fregni and Pascual-Leone, 2007). Additionally, these methods, such as transcranial current brain stimulation (tCS), arguably influence solely the targeted site of stimulation, but also exert effects on associated brain connectivity patterns (Luft et al., 2014). Since PD is characterized by abnormally exaggerated beta synchronization throughout a basal ganglia (BG)-cortical network (Eusebio et al., 2009), non-invasive stimulatory approaches could potentially be used to modulate aberrant network dynamics (Fregni and Pascual-Leone, 2007).

A few studies have suggested that non-invasive stimulation of vestibular nerves via noisy galvanic vestibular stimulation (GVS) may improve motor deficits in PD (Yamamoto et al., 2005; Pan et al., 2008; Pal et al., 2009; Samoudi et al., 2012). Noisy GVS delivers currents with randomly varying amplitudes in time to vestibular afferents and subsequently influences resting state cortical electroencephalography (EEG) activity, suggesting that cortical-subcortical connections are also modulated by GVS (Kim et al., 2013). Akin to how tCS strengthens connectivity patterns in premotor, motor, and sensorimotor areas while subjects are engaged in a finger tapping task (Polanía et al., 2011), noisy GVS hypothetically is also able to influence functional BG-cortical motor networks depending on the brain state during stimulation. It is not fully established, however, whether noisy GVS improves motor performance. Yamamoto et al. (2005) measured trunk dynamics as well as reaction time in a Go/NoGo

paradigm whereas Pan et al. (2008) measured wrist activity in akinetic PD patients. Effects of noisy GVS on postural and balance responses have also been measured in both humans and rat models (Pal et al., 2009; Samoudi et al., 2012), although none of these studies have directly investigated the effects of GVS on bradykinesia with respect to motor coordination and sensorimotor processing.

One potential way to rigorously assess the motoric effect of GVS is to utilize a visuomotor task, which is useful for understanding mechanisms that contribute to motor coordination with accuracy and stability (Ryu and Buchanan, 2012). Corrective movements and behavior are required in response to varying visual error feedback, which are important for maintaining effective perception-action or sensorimotor processing (Ryu and Buchanan, 2012). With respect to clinical significance, the ability to continually adapt one's behavior to changing environmental or sensory stimuli is particularly relevant in PD as these patients demonstrate impaired switching between motor paradigms (Engel and Fries, 2010).

In the present study, we implemented a visuomotor tracking task and investigated the effect of noisy GVS on motor performance. Our visuomotor task required subjects to respond to visual error feedback that was, unbeknownst to the subjects, either minimized to 30% of the actual error, or amplified by 200% to create the appearance of 'Better' or 'Worse' motor performance, respectively. We used linear discriminant analysis (LDA; Duda et al., 2012) to identify parameters significantly influenced by GVS and to investigate if the effects of GVS are dependent on the task conditions. We then analyzed our data using a robust multivariate linear regression method (Filzmoser and Todorov, 2011) to test if tracking movement was affected by GVS. We show that subthreshold GVS resulted in robust changes in tracking, mostly related to increased sensitivity to perceived error.

MATERIALS AND METHODS

SUBJECTS

Twelve PD subjects (10 males, 2 females; mean age 61.4 ± 6.5 years; 11 right-handed, 1 left-handed) participated in the study. None of the participants had any reported vestibular or auditory disorders. All PD subjects were recruited from the Pacific Parkinson's Research Centre (Vancouver, BC, Canada). PD subjects had mild to moderate disease severity (Hoehn and Yahr stages 1.5–2.5) with UPDRS (Unified Parkinson's Disease Rating Scale) Part III motor scores at a mean of 22.3 ± 7.8 (**Table 1**). All PD subjects were tested in the off-medicated state after a 12-h overnight withdrawal from L-dopa medication. Other medications that some subjects were on included: amantadine, ramipril, and atorvastatin.

ETHICS STATEMENT

The study was approved by the University of British Columbia Clinical Research Ethics Board. All subjects gave written, informed consent prior to participation. Research was conducted according to the principles expressed in the Declaration of Helsinki.

VISUOMOTOR TRACKING TASK

Subjects were comfortably seated 80 cm in front of a screen and performed a manual tracking task. On the screen, a target (blue) and cursor (yellow) connected by a black horizontal rod were displayed (**Figure 1**). The target box oscillated vertically up and down with the summation of two frequencies (0.06 and 0.1 Hz). Subjects controlled the cursor using a joystick with the objective of matching the horizontal position of the cursor to the target – i.e., to keep the horizontal black rod straight. The tracking error (Δ, difference between the actual positions of the target and cursor) was scaled by a factor (α) to determine the displayed position of the cursor: $\Delta \times \alpha =$ displayed visual error feedback. In the 'Better' (B) task condition, α was set to 0.3, and in the 'Worse' (W)

Table 1 | PD subjects' characteristics for behavior task.

Patient number	Age (yr)	Sex	Duration since diagnosis (yr)	UPDRS motor score	Hoehn and Yahr stage	Handedness
1	58	M	4	18	2	R
2	64	F	4	12	1.5	R
3	67	M	4	16	2	R
4	56	M	2.5	21	2	L
5	53	M	3	32	2.5	R
6	49	M	7.5	35	2	R
7	65	F	5	32	2	R
8	68	M	1.5	22	2	R
9	66	M	1	24	2	R
10	70	M	1	21	2	R
11	59	M	1.5	10	2	R
12	62	M	3.5	24	2	R

UPDRS, unified Parkinson's disease rating scale.

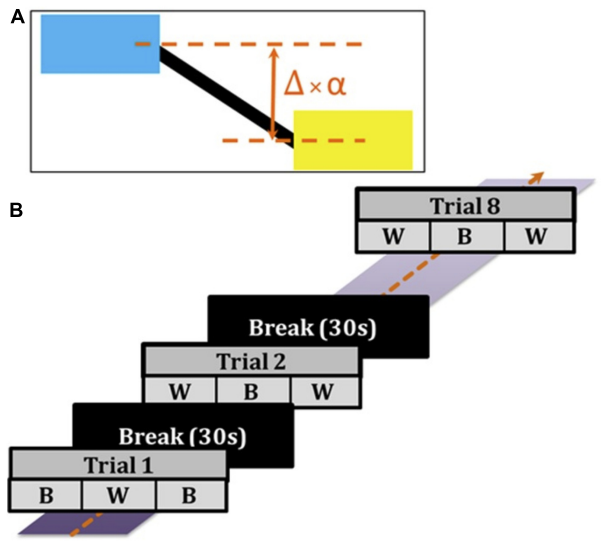

FIGURE 1 | Behavior task. (A) Subjects faced a screen with a target (blue) that moved vertically up and down, and controlled a cursor (yellow) using a joystick. The error difference (Δ) between the actual positions of the target and cursor was amplified by a scaling factor (α): $\Delta \times \alpha$ = displayed visual error feedback. In the 'Better' (B) condition, α was set to 0.3, and in the 'Worse' (W) condition, α was set to 2, such that it appeared that subjects performed better or worse respectively based on their visual error feedback. **(B)** Trials (90 s) alternated between B and W conditions (each condition 30 s). Each trial was followed by a break of 30 s until a culmination of eight trials total were completed for the experiment.

task condition, α was set to 2, such that it artificially appeared to subjects that they performed better or worse, respectively, based on their scaled error feedback.

During the experiment, subjects performed a total of eight trials. Each trial (90 s) was comprised of three alternating blocks (30 s each) of B and W conditions – with Trial 1 ordered as B-W-B and Trial 2 ordered as W-B-W (**Figure 1**). During each trial, either a subthreshold *verum* current (90% of cutaneous sensory threshold) or *sham* current stimulation was delivered. Four trials contained *verum* GVS delivery whereas the other four trials contained *sham* stimulation. Subjects were unaware of either *verum* or *sham* stimulation since the order in which stimuli were delivered was pseudorandom, and the *verum* stimulation was imperceptible to the subject. Each trial was followed by a break (30 s) to preclude a hysteretic effect carrying over to the next trial. Before starting the experiment, subjects were allowed to practice tracking the target and using the joystick as needed in at least one practice trial. Practice trials were differently structured from the eight experiment trials described above. Due to technical details of the data capture system, the cursor position was irregularly sampled at ∼55 Hz. We then resampled the data at exactly 50 Hz using linear interpolation before further analyses.

STIMULUS

Galvanic vestibular stimulation was delivered to subjects through carbon rubber electrodes (17 cm^2) in a bilateral, bipolar fashion. For bilateral stimulation, an electrode was placed over the mastoid process behind each ear, and coated with Tac gel (Pharmaceutical Innovations, NJ, USA) to optimize conductivity and adhesiveness. The average impedance of the subjects was measured around 1 kΩ. Digital signals were generated on a computer using MATLAB and converted to analog signals via a NI USB-6221 BNC digital acquisition module (National Instruments, TX, USA). The analog command voltage signals were subsequently passed to a constant current stimulator (Model DS5, Digitimer, Hertfordshire, UK), which was connected to the stimulating electrodes.

Bipolar stimulation signals were zero-mean, linearly detrended, noisy currents with a 1/f-type power spectrum (pink noise) as previously applied to PD and healthy subjects (Soma et al., 2003; Yamamoto et al., 2005; Pan et al., 2008). The stimulation signal was generated between 0.1 and 10 Hz with a Gaussian probability density, with the command signal delivered to the constant-current amplifier at 60 Hz (**Figure 2**). The stimulus was applied at an

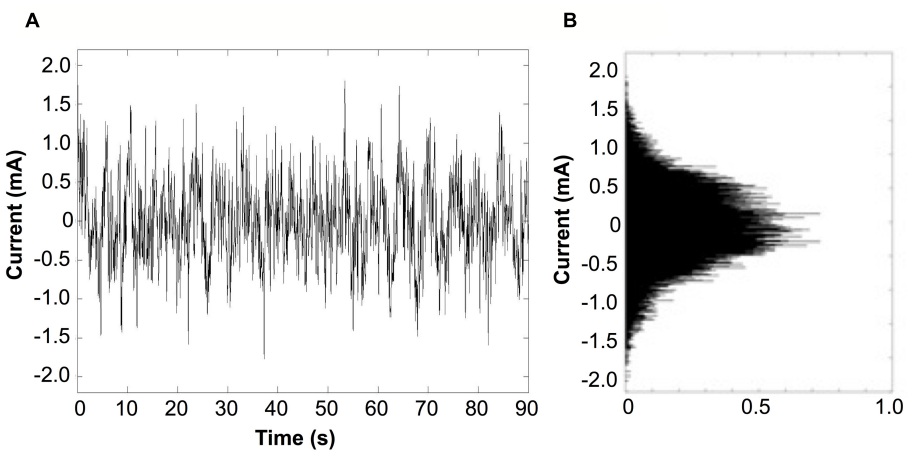

FIGURE 2 | Characteristics of the stimulus. (A) Typical recording from a subject receiving a noisy stimulus applied for 90 s duration. The stimulus presented is at the highest current intensity (current level 6), which is set to 90% of the subject's individual sensory threshold (RMS current value of 266 μA). **(B)** Probability density function of the stimulus current follows a Gaussian distribution.

imperceptible level to avoid effects by general arousal and/or voluntary selective attention, with the current level individually determined according to each subject's cutaneous sensory threshold.

Since perception of GVS is inherently subjective, we utilized systematic procedures that have been previously used in determining subliminal current levels for both GVS and transcranial stimuli (Hummel et al., 2005; Utz et al., 2011; Wilkinson et al., 2012). Starting from a basal current level of 20 μA, noisy test stimuli were delivered for 20 s periods with gradual stepwise increases (20 μA) in current intensity until subjects perceived a mild, local tingling in the area of the stimulating electrodes. As performed previously, a threshold value was defined once subjects reported a tingling sensation (Utz et al., 2011; Wilkinson et al., 2012), which lasted for the duration of the test stimulus. The current level was then decreased each time by one level until sensation was no longer reported during delivery of test stimulus pulses, and increased by one step in current intensity to confirm threshold. Each delivery of a test stimulus was followed by a period of no stimulation for at least 30 s to preclude a hysteretic effect carrying over to the next test stimulus. Subjects were blind to the onset and duration of test stimuli, as well as the threshold-testing scheme. After completing the threshold test and throughout the experiment, stimuli were delivered at subthreshold intensity (190–900 μA), which is achieved at 90% of the determined cutaneous sensory threshold value.

BEHAVIORAL DATA ANALYSIS

We employed both exploratory and hypothesis-driven analysis methods to analyze the behavioral data. We initially analyzed the data on a subject-by-subject basis as we were unclear whether or not there would be substantial intersubject variability to GVS response. LDA was first used to see if tracking behavior could be reliably discriminated depending upon whether GVS was applied or not. We derived a GVS linear discrimination function, g(X), to create maximum separation between means of the projected classes with minimum variance within each projected class:

$$\mathrm{g}(\mathbf{X}) = w_1\boldsymbol{X_1} + w_2\boldsymbol{X_2} + \cdots + w_{21}\boldsymbol{X_{21}} + \omega_0 = \boldsymbol{w^t X^t} + \omega_0 \quad (1)$$

where $\boldsymbol{X} = [\boldsymbol{X_1}\ \boldsymbol{X_2}\ \ldots\ \boldsymbol{X_{21}}]$ is a input data matrix in which each column represents an independent variable, $\boldsymbol{w} = [w_1, w_2, \ldots, w_{21}] \in \mathbb{R}^{21}$ the weight vector containing linear coefficients of the variables in the data matrix $\boldsymbol{X}$, and ω_0 the bias-weight. LDA was applied to the "Better" and "Worse" conditions separately.

For this exploratory part of the analysis, we included linear (first-order) and non-linear (second- and third-order) combinations of variables in the GVS discriminant function (**Table 2**). During the experiment, we varied the phase of the initial target trajectory not only between subjects but also between the trials to prevent the subjects from easily predicting upcoming target movement. Therefore, variables from X_1 to X_9 were included as nuisance variables in the LDA to account for the target differences.

To test for significance of the LDA results, we employed bootstrapping techniques. We permuted the GVS labels (on/off) and then re-computed the LDA function with the permuted data.

Table 2 | Variables in linear discriminant analysis (LDA) model.

Notation	Variables
X_1, X_2, X_3	$T(t), T(t)^2$, $T(t)^3$
X_4, X_5, X_6	$V_T(t)$, $V_T(t)^2$, $V_T(t)^3$
X_7, X_8, X_9	$A_T(t)$, $A_T(t)^2$, $A_T(t)^3$
X_{10}, X_{11}, X_{12}	$D(t) - T(t)$, $\{D(t) - T(t)\}^2$, $\{D(t) - T(t)\}^3$
X_{13}, X_{14}, X_{15}	$V_D(t) - V_T(t)$, $\{V_D(t) - V_T(t)\}^2$, $\{V_D(t) - V_T(t)\}^3$
X_{16}, X_{17}, X_{18}	$D(t + \Delta t) - D(t)$, $\{D(t + \Delta t) - D(t)\}^2$, $\{D(t + \Delta t) - D(t)\}^3$
X_{19}, X_{20}, X_{21}	$V_D(t + \Delta t) - V_D(t)$, $\{V_D(t + \Delta t) - V_D(t)\}^2$, $\{V_D(t + \Delta t) - V_D(t)\}^3$

T, target position; V_T, target velocity; A_T, target acceleration; D, displayed cursor position; V_D, displayed cursor velocity; t, time index, and Δt, reaction delay of 0.5 s (Jordan et al., 1992).

This was repeated 1000 times. Any weight value from the original LDA function g(X) whose absolute value was greater than all the weights computed from the permuted data was considered to be significantly influenced by GVS.

In addition, a multivariate linear regression model was used to test the hypothesis that GVS had a significant effect on cursor position during tracking. As the traditional least squares regression may be sensitive to noisy and gross errors (Akkaya and Tiku, 2008), we chose a robust regression method to analyze our data ("robustfit" function in MATLAB). This method is known to be robust to outliers utilizing an iteratively reweighted scheme to deweight the influences of outliers. With cursor position as a response variable (Y_i), the following regression model was proposed:

$$Y_i = \boldsymbol{A_i}\boldsymbol{\beta} + \boldsymbol{\varepsilon_i} \quad (2)$$

where for each data point i we have the vector of independent variables $\boldsymbol{A_i} = [A_{i1}, \cdots, A_{i5}]$, the vector of regression coefficients solved by a bisquare weighting function $\boldsymbol{\beta}$, and the residual $\boldsymbol{\varepsilon_i}$ (assumed to be independent and identically distributed Gaussian). The selected independent variables are summarized in **Table 3** (note that A_1, A_2 and A_3 are same as the variables X_1, X_4 and X_{10} in eq.1, respectively). The categorical variable of GVS was denoted with either 0 (GVSoff) or 1 (GVSon). We tested for significance

Table 3 | Estimated coefficients in the robust regression model (eq.2) and the *p*-values.

Variables (*A*)	Coefficient estimates (*β*)	*p*-value
Target position (A_1)	1.00	0.0000
Target velocity (A_2)	−7.79e-02	0.0000
Displayed cursor position – target position (A_3)	5.01e-01	0.0000
Cursor velocity – target velocity (A_4)	−1.60e-02	0.0002
GVS (A_5)	3.99e-05	0.0410

$R^2 = 0.8811$.

of the coefficients under the null hypothesis that the coefficient estimates were equal to zero.

For a signal-to-noise ratio (SNR) analysis, we utilized "snr" function in MATLAB to calculate SNR of cursor trajectories. This examines the fundamental frequencies of the tracking trajectory plus the next six harmonics, and assumes that any power in the spectrum than these peaks are "noise."

RESULTS

RESULTS OF LDA IN WORSE CONDITION

Coefficients of GVS discriminant function (eq.1) were calculated for each subject and are plotted as black lines in **Figure 3**. For clarity, nuisance variables related to absolute target position (i.e., X_1–X_9) are not shown. The 1000 sets of linear coefficients generated from the bootstrapping are depicted as blue lines. In most subjects, the coefficients w_{10}, w_{11}, and w_{12} of g(X; representing linear and higher powers of the perceived error between the target and the displayed cursor position) were robustly modulated by GVS. In addition, displayed cursor velocity (w_{16} or w_{17}) and acceleration (w_{19}, w_{20}, or w_{21}) were also found to be significantly affected by GVS across subjects.

RESULTS OF LDA IN BETTER CONDITION

Figure 4 shows the LDA results in the better condition. As before, coefficients w_{10}, w_{11}, and w_{12} were significant among all the subjects. In addition, 10 out of 12 subjects showed significant w_{18} weightings. Other coefficients were not robustly seen in all subjects. For example, unlike the LDA results of the Worse condition, displayed cursor acceleration (w_{19}, w_{20}, or w_{21}) was no longer significantly influenced by GVS in the Better condition.

RESULTS OF ROBUST REGRESSION MODEL

Table 3 is the coefficient estimates of the variables of the multivariate regression model (eq.2) and their p-values. The computed R^2 of the regression model was 0.8811. GVS was significantly associated with cursor position across all subjects ($p < 0.05$).

EFFECT OF GVS ON CURSOR OVERSHOOTING

In order to get an intuitive interpretation of GVS effects, we calculated the GVS discriminant function values (eq.1) for each subject. We used data from trials 1 and 7 for the calculation as these two trials had identical phases of the trajectories, with a difference in whether or not GVS was delivered (GVSon for trial 1). Then, Δg was computed by subtracting the function values of trial 7 from trial 1. By plotting Δg, we could not only locate GVS effects on the cursor trajectory but also directly make visual comparison of the cursor movement in the identified location. **Figure 5** shows target trajectory, cursor trajectory and Δg for each subject.

The effect of GVS was greatest near sinusoidal peaks. This trend was found in most of the subjects regardless of how well the subjects tracked the target. For instance, subject 5 tracked the target relatively better compared to the other subjects, and Δg was significant around at 5, 20, 65, and 80 s. Subjects 11 and 12 performed the tracking task poorly, but the GVS effects still appeared near sinusoidal peaks.

One of the noticeable features on the peaks is a degree of overshooting of cursor trajectories. To assess a possible relationship to GVS stimulation, we compared the difference between the cursor position and the target on the peaks. **Figure 6** shows a representative example of cursor overshooting near sinusoidal peaks in target. The peaks in cursor appeared with some lagged

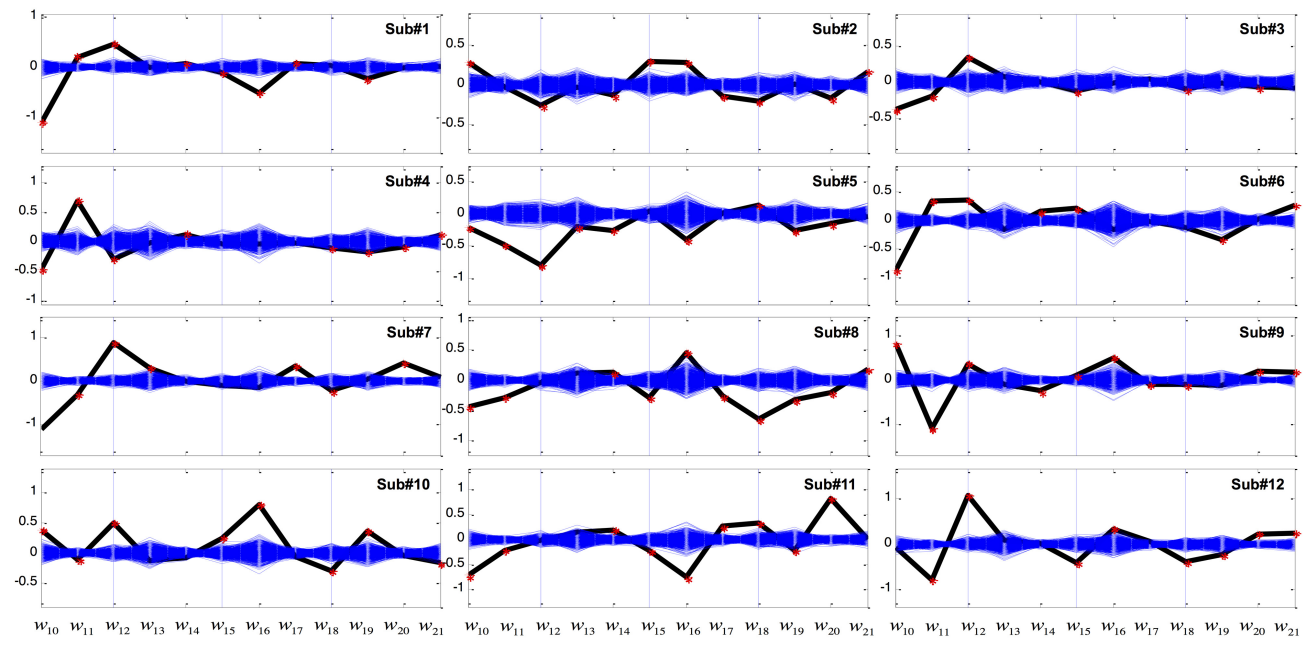

FIGURE 3 | Coefficients of the variables of the linear discriminant function in the Worse condition. The x-axis represents variables from X_{10} to X_{21} in **Table 2** while the y-axis represents weight (w) value. The computed coefficients are depicted as black for the GVS discriminant function and blue for bootstrapping. Red asterisks denote coefficients that are outside the 95% confidence interval of bootstrapping.

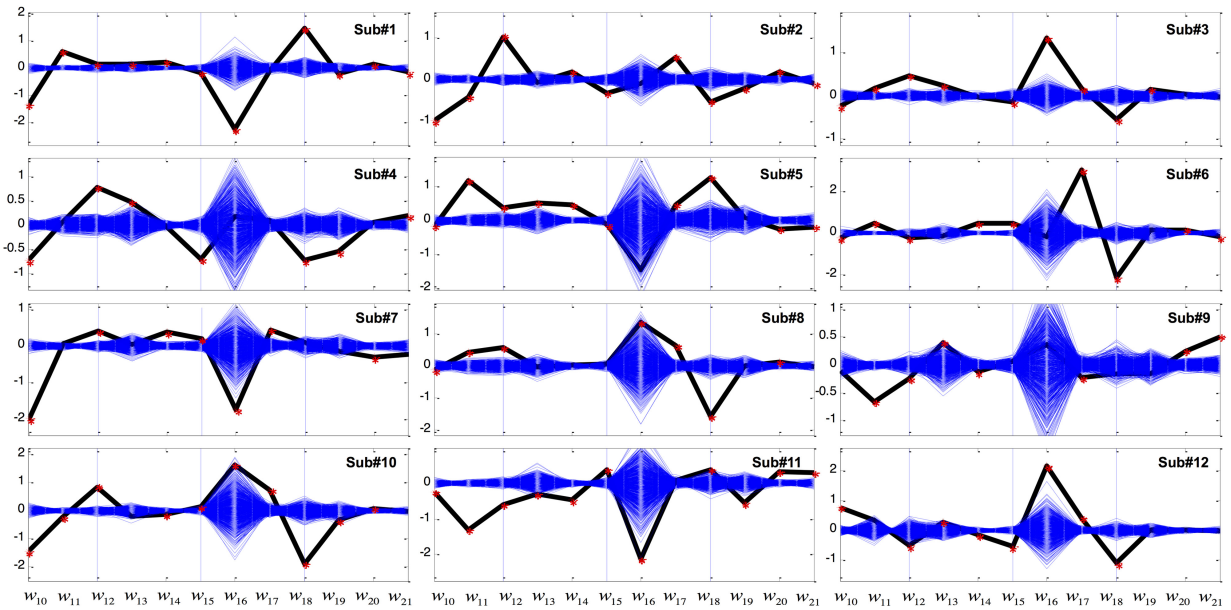

FIGURE 4 | Coefficients of the variables of the linear discriminant function in the Better condition. The *x*-axis represents variables from X_{10} to X_{21} in **Table 2** while the *y*-axis represents weight (w) value. The computed coefficients are depicted as black for the GVS discriminant function and blue for bootstrapping. Red asterisks denote coefficients that are outside the 95% confidence interval of bootstrapping.

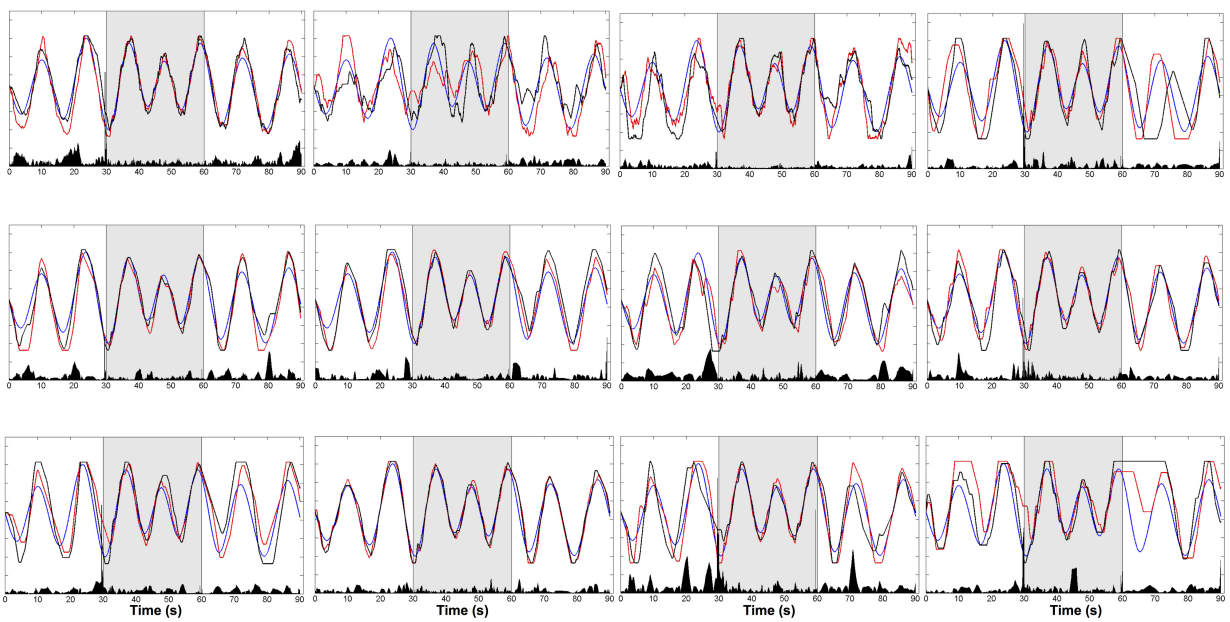

FIGURE 5 | Trajectories of target (blue) and cursor (GVSon: red, GVSoff: black) and Δg (black bar in the bottom). Δg was computed by subtracting the linear discriminant function values of trial 7 (GVSoff) from trial 1 (GVSon). The trials alternated between W-B-W conditions (each condition 30 s).

time (Δt). The amplitude of the target peaks was subtracted from the cursor peaks, and the difference (Δd) was defined as cursor overshooting. Cursor peak was defined when the cursor position was at its max/min point. Cursor overshooting was calculated for all trials and subjects, then averaged depending on the task conditions and presence of GVS stimulation as shown in **Table 4**. The *p*-value was calculated from ANOVA of the means between GVSon and GVSoff (i.e., a single, two-level factor).

In Worse condition, the subjects tended to overshoot significantly less on the lower peaks while stimulated by GVS. On the upper peaks, the mean overshooting of GVSon was also smaller

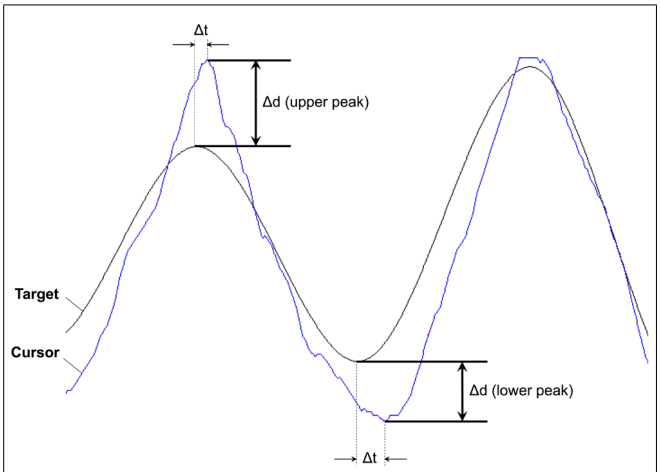

FIGURE 6 | Representative example of cursor overshooting on upper and lower peaks from Subject 1 Cursor overshooting (Δd) was calculated as cursor position – target position. Δt represents time difference between peaks in cursor and target trajectories.

Table 4 | Means of cursor overshooting on sinusoidal peaks and ANOVA results.

	Lower peak			Upper peak		
	GVSon	GVSoff	*p*-value	GVSon	GVSoff	*p*-value
Worse	−0.0517	−0.0714	0.0036	0.0695	0.0784	0.22
Better	−0.0946	−0.0451	0.0038	0.0890	0.0690	0.14

than GVSoff, but the difference was not significant. In Better condition, however, there was an increasing tendency for cursor overshooting with stimulation.

EFFECT OF GVS ON SNR OF CURSOR TRAJECTORY

Movement variability is another important feature to characterize the tracking performance. Particularly, in goal-directed behavior, the variability originates from collateral movement to the main goal of a task. In this sense, the cursor trajectories in our tracking test can be seen to a combination of two components. One is the primary movement whose form is similar to the target trajectory, and the other is submovement that may appear as noise superimposed on the primary movement. In order to investigate if GVS had affected movement variability of the subjects, we calculated SNR of cursor trajectories and compared differences in between GVSon and GVSoff conditions. As shown in **Figure 7**, the mean SNR of 12 PD subjects was 27.6 when GVS was applied, which was significantly greater than 21.3 in GVSoff condition ($p < 0.05$).

DISCUSSION

Our results demonstrate that noisy GVS robustly influences motor tracking performance in PD patients off dopaminergic medication. Motor improvements are consistent with results previously reported in hemiparkinsonian rats (Samoudi et al., 2012) whereby

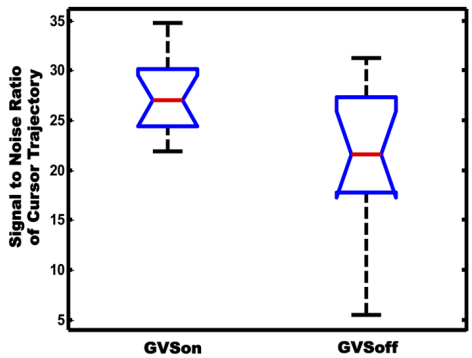

FIGURE 7 | Comparison of SNR of cursor trajectories between GVSon and GVSoff conditions.

GVS with a 1/f power density improved rod performance. Previously, we demonstrated that noisy GVS has the ability to modulate synchronization of broadband EEG oscillations in healthy subjects (Kim et al., 2013). Our recordings of EEG rhythms were observed at resting-state, suggesting that noisy GVS was able to modulate cortical activity and presumably connected subcortical-cortical projections. In this study, we observed a functional effect of GVS on sensorimotor processing and motor performance in a visuomotor task, suggesting that noisy vestibular stimulation modulates motor networks in PD subjects.

Our results seem to indicate that noisy GVS affects the sensitivity of motor responses (in this case, joystick-controlled cursor position) to visualized error (displayed cursor position – target position). We do not believe that our observed results are the consequence of an attentional or general arousal effect, such as through activation of the reticular activating system. The imperceptible nature of our stimulus, which subjects were not aware of throughout the experiment trials, precludes this issue which is present with other forms of minimally invasive stimulation methods (Fuentes et al., 2009).

Depending on the stimulus parameters (i.e., current intensity, frequency, signal shape), GVS is known to induce a broad range of effects, including eye movements, postural control and movements (Fitzpatrick and Day, 2004). Therefore, one interpretation of our results may include the confounding effects of nystagmus and/or ocular torsion through activation of the vestibulo-ocular reflex (VOR; Zink et al., 1998). Since subjects rely on visual error feedback, ocular torsion would potentially hamper the perceived error feedback through a subjective tilt in the visual perceptual field (Zink et al., 1998). However, we note that our stimulus levels were weak, subthreshold currents with the highest current delivered at around 140 ± 113 μA, whereas the preferred GVS current intensities for inducing ocular torsion and subsequent perceptual tilts through GVS are much higher at around 1–3 mA (Zink et al., 1998). Therefore, we presume that our subthreshold stimulus was not strong enough to notably induce confounding visual effects and corollary perceptual changes in our experiment.

Noisy GVS is known to modulate EEG spectral power. Wilkinson et al. (2012) have demonstrated that noisy GVS is able to

modulate the EEG spectral power during a face processing task. Our previous study has demonstrated that noisy GVS is able to modulate the EEG synchrony patterns in healthy subjects (Kim et al., 2013). Altogether, these findings combined with our present results suggest that noisy GVS is able to modulate oscillatory activity in resting and task-related networks, which involve sensorimotor processing in our particular study.

The motoric effects of GVS may be related to modulation of oscillations related to integration of information and error-processing. Since perceived error (i.e., the error between the target and the displayed cursor position) was robustly detected by the LDA analysis, fronto–midline (FM) theta may be a candidate oscillation to be modulated by GVS in PD subjects. FM-theta shows an increased amplitude during tasks requiring concentration (Mitchell et al., 2008), which is related to error-related negativity (ERN), an event-related potential seen after errors are made. FM-theta may represent a universal mechanism for action monitoring with the midcingulate cortex acting as hub for the integration of information (Cavanagh et al., 2012). Thus, our results suggest that GVS may regulate FM-theta activity in PD subjects.

The increased SNR shown in **Figure 7** suggests that application of noisy GVS may have increased synchronization in neuromotor system via stochastic facilitation. Stochastic facilitation is a term to describe phenomena where stochastic biological noise elicits functional benefits in a non-linear system such as the nervous system (McDonnell and Ward, 2011). Several studies have reported that a presence of additive noise allows a weak input signal to be better detected, resulting in an increase in SNR in EEG (Galambos and Makeig, 1992; Srebro and Malladi, 1999; Elias et al., 2003; Kitajo et al., 2007; Keita et al., 2008; Ward et al., 2010; Doren et al., 2014) and sensorimotor performance (Ignacio et al., 2012). These findings suggest that noisy GVS input may also be able to modulate detection and transmission of the sensorimotor system via stochastic facilitation, resulting in an increase in synchronization of the neuromotor system. However, a further investigation is required to elucidate whether the synchronization is limited to cortical areas or if it could give rise to corticomuscular synchronization (Ignacio et al., 2012).

We further speculate that our results may be at least partly explained by modulation of cortico-BG rhythms involved in sensorimotor processing. Growing observations suggest a concept that the BG regulates action motivation or response 'vigor' (Niv et al., 2007; Salamone et al., 2009) as well as the speed and size of movement (Spraker et al., 2007; Thobois et al., 2007). Deficient scaling of the initial burst of earliest agonist muscle activity (EMG) to meet the demands of a motor task is frequently observed in clinical disorders of the BG, such as PD. The link between motivation and movement gain may be universally weakened in Parkinsonian subjects (Ballanger et al., 2006; Thobois et al., 2007). We thus speculate that GVS may also correct deficient vigor caused by BG dysfunction through modulation of pathological brain rhythms.

We note that we used a single noisy stimulus for all subjects. However, the results shown in **Figure 3** also emphasize the importance of looking at patient-specific stimuli. For instance, the coefficients regarding the difference between cursor and target velocities (w_{13}, w_{14}, and w_{15}) were found to be significant in some subjects, but were indistinguishable from bootstrapping for the rest subjects.

Finally, we note that GVS had fewer effects in the Better condition compared to the Worse condition. Presumably, subjects would have made fewer corrective movements in the former condition. This raises the possibility that GVS may also depend upon the number and form of corrective submovements. As submovements were not captured by the global LDA and multivariate regression methods used here, this warrants further investigation.

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Preserving cortico-striatal function: deep brain stimulation in Huntington's disease

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Huntington's disease (HD) is an incurable neurodegenerative disease characterized by the triad of chorea, cognitive dysfunction and psychiatric disturbances. Since the discovery of the HD gene, the pathogenesis has been outlined, but to date a cure has not been found. Disease modifying therapies are needed desperately to improve function, alleviate suffering, and provide hope for symptomatic patients. Deep brain stimulation (DBS), a proven therapy for managing the symptoms of some neurodegenerative movement disorders, including Parkinson's disease, has been reported as a palliative treatment in select cases of HD with debilitating chorea with variable success. New insights into the mechanism of action of DBS suggest it may have the potential to circumvent other manifestations of HD including cognitive deterioration. Furthermore, because DBS is already widely used, reversible, and has a risk profile that is relatively low, new studies can be initiated. In this article we contend that new clinical trials be considered to test the effects of DBS for HD.

Keywords: deep brain stimulation, Huntington's disease, globus pallidus, striatum, cognition, chorea

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Preserving Cortico-Striatal Function: Deep Brain Stimulation in Huntington's Disease

Few conditions in medicine present patients and their families the challenges of Huntington's disease (HD). Because it is a heritable disease, the majority of individuals at risk are exposed to a turbulent environment with a parent diagnosed with HD and faced with the reality of suffering a similar fate. At-risk patients have the option to learn if they have the disease and then must confront the sad truth that the disease will end in neurologic disability and premature death. For those who elect not to be tested, the specter of developing symptomatic HD still looms large. This in part contributes to the increased risk of suicide during early stages and engenders fear and desperation that perpetuates itself with time as families search for answers (Meiser and Dunn, 2000). This psychological burden, coupled with the absence of any promising interventions, contributes to low predictive testing rates and the potential to adopt overly optimistic beliefs about one's future, which at times may have undesirable consequences from a medical or economic standpoint (Oster et al., 2013).

It is estimated that 30,000 individuals in the United States alone have manifest symptoms of HD, with twice as many additional individuals yet to manifest symptoms. Extensive efforts

on the part of researchers, emboldened by these unfortunate facts, identified the genetic basis of HD in the early 1990's. Since then, the effort to find a cure has accelerated, although to date only one therapeutic agent has been approved for clinical use. Physicians are therefore left to consider off-label uses of existing therapies. Deep brain stimulation (DBS) has been used in HD as a treatment for disabling chorea but targeted stimulation may be a potential consideration to palliate symptoms of HD.

Several longitudinal studies have contributed to the current understanding of the natural history of HD (Paulsen et al., 2008; Ross and Tabrizi, 2011; Ross et al., 2014). The mean age of onset is 40 with an additional 20 years of life expected after the disease manifests (Tabrizi et al., 2011). Onset is defined with the emergence of motor symptoms. Chorea—abrupt, random, involuntary movements—is the hallmark of HD. These movements often intensify before being replaced with voluntary motor deficits. The cognitive features of HD consist of executive dysfunction, visuospatial dysfunction, cognitive slowing, and loss of mental flexibility. Evidence suggests that cognitive dysfunction may parallel (or precede) the emergence of motor deficits (Paulsen and Long, 2014). The psychiatric manifestations vary widely, ranging from mood disturbances to obsessional anxiety and, rarely, psychosis. Furthermore, limbic dysfunction, in the setting of cognitive inflexibility and poor insight, contributes to a 'dysexecutive syndrome', characterized by perseveration, apathy, impulsivity and aggression. Non-pharmacologic interventions may be helpful in early stages but tend to become less effective as the disease progresses. Tetrabenazine is the only FDA-approved agent for the treatment of the chorea. Psychiatric symptoms are managed similarly to the general population. Cognitive symptoms are typically resistant to intervention. Biomarkers that correlate to disease stages have not yet been defined, although promising considerations in premanifest individuals have been identified (Paulsen et al., 2014).

Pathogenic Mechanisms of HD

HD exhibits autosomal dominant inheritance and is equally prevalent in men and woman. In those who inherit the mutation, a cytosine-adenosine-guanine (CAG) repeat expansion is added to the IT15 huntington (HTT) gene on the short arm of chromosome 4 (Raymond et al., 2011). Affected individuals with the mutated form have between 36 and 121 CAG repeats in the coding region that translate into a polyglutamine expansion. The age of onset of motor symptoms inversely correlates with the number of repeated sequences (Ross et al., 2014). In healthy persons, HTT encodes a protein (huntingtin) responsible for synaptic vesicular transit and other cellular functions that when absent leads to *in utero* death (Cepeda et al., 2007). For example, wild type huntingtin contributes to the cortical production of brain derived neurotrophic factor (BDNF) before the latter's downstream support of striatal neurons (Zuccato et al., 2010). In those with the mutation, glutamine residues accumulate and the mutant HTT protein disrupts cellular signals and homeostasis decades before symptoms emerge. The mutation is detectable in nervous tissue diffusely; however, the disease is uniquely characterized by its expression in the medium spiny neurons (MSNs) found in the caudate, putamen and cortical pyramidal cells. The eventual death of these MSNs is the pathological hallmark of the structural damage demonstrated in HD (Georgiou-Karistianis et al., 2013). The precise cascade of events that leads to neurodegeneration is still largely unknown (Raymond et al., 2011).

MSNs account for 90% of all neurons in the striatum and are its only output source (Murer et al., 2002). There are two subtypes of MSNs that are differentiated by the peptides co-expressed; the receptor subtypes and the target to which they project. These GABAergic MSNs exert their effect via a direct or indirect pathway. MSNs in the indirect pathway (striaopallidal, D2 receptors) project to the external segment of the globus pallidus (GPe) and subthalamic nucleus (Cepeda et al., 2007). These indirect pathway neurons are the first cell population to succumb in HD and are implicated in the hyperkinesia that heralds the onset of the disease. MSNs in the direct pathway (striatonigral, D1 receptors) project to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulatea (SNr; Cepeda et al., 2007). Degeneration of direct pathway MSNs, and the resulting loss of substance P, may contribute to late stage motor features characterized by impaired voluntary movement (Raymond et al., 2011). This transition from hyperkinesia to akinesia during the natural history of the disease may confound the results of interventions aimed at arresting or controlling chorea.

Impaired dopamine homeostasis is another consequence of the mutation that contributes to the impaired information processing from cortical inputs to the striatum (André et al., 2010). Dopaminergic neurons projecting from the substantia nigra pars compacta, and to a lesser degree the ventral tegmental area (VTA), to the dorsal striatum regulate glutamate sensitivity as well (dorsal circuit). Indirect pathway MSNs express D2 receptors whereas D1 receptors are more abundant in direct pathway MSNs. Degeneration of these nigrostriatal dopaminergic neurons are observed in HD and may contribute to late onset akinesia (André et al., 2010; Raymond et al., 2011). Conversely, presynaptic hyperactivation of the nigrostiatal pathway may elicit the characteristic chorea of early stage disease (André et al., 2010). Agents affecting dopamine (DA) transmission are used to modulate HD symptoms with some effect. DA may facilitate the "upstate" or depolarized state that enables encoding of specific motor tasks routed by the corticostriatal pathway (Murer et al., 2002).

The primary inputs to the MSNs are glutamatergic projections from the neocortex. Cortical neuron death is also observed in HD, especially in layers III, V and VI. The cell death is profound enough to be observed on gross pathological specimens and predates the onset of motor symptoms. One hypothesis is that excitotoxicity at the cortico-striatal synapses underpins HD (Cepeda et al., 2007). This is supported by evidence that increased release of glutamate from cortical projections, together with reduced uptake from the synaptic cleft by glial cells and enhanced striatal sensitivity to glutamate contributes to an

amplified affect (Wójtowicz et al., 2013). In mouse models of HD, down-regulation of GLT1 has been demonstrated (Liévens et al., 2001). GLT1, a sodium-dependent glutamate transporter, ordinarily serves to remove extracellular glutamate and limit excitotoxicity. This down-regulation, together with NMDA-R hypersensitivity, increases intracellular calcium and induces an apoptotic cascade in HD.

Aspiny cholinergic, fast spiking, interneurons that co-express parvoalbumin are the main inhibitory neurons within the striatum (Russo et al., 2013). Theses interneurons are typically preserved until the late stages of the disease and are at least partly responsible for information processing and integration in the normal striatum (Raymond et al., 2011). Although, the death of the interneurons lags behind the MSNs, the dystonia that is especially pronounced in early onset and juvenile HD may be related to interneuron death (Reiner et al., 2013).

Abnormal Electrophysiology in HD

Under normal conditions, the ventral, dorsolateral (motor) and dorsomedial (associative) striatum are both activated simultaneously during specific task learning (Williams and Eskandar, 2006; Gale et al., 2014; Thorn and Graybiel, 2014). As a behavior becomes habitual, the association between striatal components decouples and the ventral (Gale et al., 2014) and motor striatum emerges while the activity of the associative striatum, now redundant, recedes (Williams and Eskandar, 2006; Thorn and Graybiel, 2014). In the ventral striatum, the learning related facilitation of activity is thought to represent the increased expectation of reward for the execution of specific stimulus-motor behaviors (Gale et al., 2014). Thus, under normal conditions, it is thought that the ventral striatum provides the motivation to engage in reward obtaining behaviors. In HD, the depressive and limbic symptoms may be related to motivational changes brought on by dysfunction of striatal MSNs and/or dopamine de-innervation (via dopamine cell loss of the SNpc and VTA). In the dorsal striatum, once a task is learned, the specific motor sequences or chunks are organized within the basal ganglia as a concatenation of neuronal activity played out in the direct and indirect pathway. Co-activation of these pathways facilitates the desired movement by suppressing unwanted movements (indirect) and expressing the specific motor chunk (direct pathway) (Jin et al., 2014). Near limitless combinations of nested oscillating frequencies are able to associate with these specified action sequences. Normally, when an action is queued, an assembly of neurons transitions to the upstate, enabling the asynchronous, specified action to emerge (Stern et al., 1998). However, in HD, the bidirectional cortico-striatal network is no longer able to precisely orchestrate action as nested frequencies uncouple (Miller et al., 2011). Together with the thalamocortical network, which helps set the membrane potential of the MSNs, the system becomes deregulated. As redundancies in the system also dissociate, the behavior chunk fails.

This high degree of coordination needed to facilitate a desired movement is evident when studied on a smaller scale. In mouse models of HD, widespread electrophysiologic dysfunction at the neuronal level is observed. The MSNs demonstrate a depolarized resting membrane potential. This induces hyper-excitability of the depolarization dependent NMDA receptor in response to glutamate. The overactive cells create an energy sink that may lead to cellular death (Rebec et al., 2006). Similar findings are noted in cortical pyramidal cells. As the disease progresses, the overactive cortico-striatal pathway eventually becomes less active and cortical synaptic inputs are lost (Cepeda et al., 2003).

Normalizing large-scale nested oscillations or stabilizing more localized dysfunctional units in HD is challenging. To achieve this, establishing how fundamental frequencies within the striatum evolve throughout the course of HD will be paramount. Recordings from the dorsal striatum in one study of freely moving normal rats demonstrated LFPs in the 1–30 Hz range with a relatively isolated peak at 50–55 Hz (Masimore et al., 2004). Still, LFPs in HD patients have not been well characterized (Estrada-Sánchez and Rebec, 2013). Once known, an attempt to tune the local frequency with electrical stimulation (ES) to regulate function may be possible.

In HD, re-entrainment of the striatum through ES of both the direct and indirect pathway, may repair learning deficits or reduce the rate of loss of existing habitual circuits. ES may also be able to partially restore the energy imbalance by reducing the hyper-excitable state, consequently preserving cortical inputs. Interestingly, in some animal models of HD, the cortex assumes a hyper-excitable state only after the disease has progressed. This finding contrasts with the observations in MSNs but may mark an identifiable time point for intervention (Cummings et al., 2009).

Deep Brain Stimulation for HD

There are several reports describing the use of DBS in HD when debilitating chorea predominates in the presence of atrophy and structural changes. We must be cautious in the interpretation of these studies based on the heterogeneity (**Table 1**). The target most often selected was GPi and DBS was primarily offered to control medically refractory chorea in most cases; although the progression to hypokinesia later in the disease can sometimes complicate interventions (Reiner, 2004). Although cognition was either not addressed or mentioned only in brief, these studies serve as a starting point for the next generation of DBS therapies for HD.

In one of the earliest published reports, bilateral GPi leads were implanted in a patient with pharmacologically-refractory HD chorea (Moro et al., 2004). 40 Hz stimulation improved the chorea and dystonia in this patient. The effect was enhanced at higher frequencies (130 Hz) but this exacerbated the bradykinesia, corroborating findings in other studies. Positron Emission Tomography (PET) studies in this patient also demonstrated increased cerebral blood flow in the supplementary motor area, anterior cingulate cortex and sensorimotor cortex with "ON" stimulation only. It is unclear what, if any, cognitive gains may have been facilitated by DBS. In the wake of the success treating this initial patient, others followed, publishing their findings after bilateral GPi DBS for HD

TABLE 1 | Summary of published deep brain stimulation reports for HD.

	Target(s)	*N*	Ages(s) at surgery (years)	Approximate disease duration prior to DBS (years)	CAG repeat length(s)
Moro et al. (2004)	GPi	1	43	8	-
Hebb et al. (2006)	GPi	1	41	13	47
Biolsi et al. (2008)	GPi	1	60	10	44
Fasano et al. (2008)	GPi	1	72	17	-
Ligot et al. (2011)	GPe	5	41–60	2–5	41–53
Kang et al. (2011)	GPi	2	57	10	42
			50	5	41
Groiss et al. (2011)	GPi	1	65	-	-
Spielberger et al. (2012)	GPi	1	30	9	58
Cislaghi et al. (2013)*	GPi	1	27	12	74
Huys et al. (2013)	GPi	1	40	3	-
Velez-Lago et al. (2013)	GPi	2	34	7	60
			25	6	68
Gonzalez et al. (2014)	GPi	7	30–78	3–8	40–50
Gruber et al. (2014)	STN and GPi	1	41	9	49
Beste et al. (2014)	GPe	2	57	-	42
			32		53

Westphal variant; (-) indicates data was not found or reported.

with mixed, but generally favorable, results (Hebb et al., 2006; Spielberger et al., 2012).

Biolsi et al. described a patient with bilateral GPi DBS implantation for chorea, which also had moderate subcortical cognitive dysfunction at the time of surgery (Biolsi et al., 2008). Four years later, the cognitive dysfunction remained stable and the patient was still able to perform complicated motor tasks. DBS in this case reduced the chorea and may have been neuroprotective, although his disease progression had been noted to be slow even prior to DBS. In another case, bilateral GPi DBS was performed which demonstrated global progressive cognitive decline on serial testing. He, like others, developed bradykinesia after DBS that prevented stable ambulation (Fasano et al., 2008). In two other patients who underwent bilateral GPi, chorea was improved at 2 years but cognitive decline continued, suggesting DBS was unable to halt progression of cognitive dysfunction (Kang et al., 2011).

Another report of two patients who underwent DBS of the GPi as a palliative treatment for disabling motor symptoms was recently published (Velez-Lago et al., 2013). In one patient, for whom chorea was the predominate symptom, DBS reduced a chorea subscore on the Unified HD Rating Scale. In the second patient, DBS was offered as a treatment of generalized, non-fixed dystonia. This failed to improve her dystonia, and the devices were eventually turned off. Although GPi DBS is a well-established treatment for primary generalized dystonia, the dystonic symptoms in HD are unique and appear to reflect the loss of direct pathway striatal neurons in advanced disease.

In the largest published series to date, seven patients with refractory chorea were treated with bilateral GPi DBS between 2008 and 2010 (Gonzalez et al., 2014). Similar to the other studies, chorea improved on average 60% at 1 year but a favorable improvement on the total motor score was not observed (Gonzalez et al., 2014). Importantly, DBS did not alleviate dystonia; while deactivation of stimulation reactivated chorea, indicating that, as for other movement disorders, the effects on motor symptoms depend on continuous stimulation.

Gruber et al. implanted a patient using simultaneous STN and GPi DBS in an attempt to recalibrate the direct and indirect pathways. This strategy minimized the bradykinesia observed following GPi stimulation alone (Gonzalez et al., 2014). Not surprisingly, when STN was used alone, chorea was not sustainably improved (Gruber et al., 2014).

Because of its role in error processing control, the GPe is another potential target for DBS in patients with HD exhibiting cognitive dysfunction. Error processing control, a measure of negative feedback that updates a behavioral action in real time, is believed to underlie early executive dysfunction in HD (Smith et al., 2000). Temel et al. tested DBS of the globus pallidus externus in a transgenic rat model of HD to evaluate the effect on motor and cognitive function (Temel et al., 2006). Cognitive function was measured by performance on a choice reaction time test. Transgenic rats will prematurely release a lever associated with a food reward compared to controls. This indicates that transgenic rats are unable to suppress the unwanted response. In both wild type rats and transgenic rats, DBS improved performance on the choice reaction time test relative to preoperative testing. Although the number of animals tested was small, this study suggests DBS restores unwanted response inhibition in the indirect pathway--a necessary precursor for executing learned behavior in the co-activation model.

In part, based on these results, Ligot et al. proposed that inhibitory stimulation of GPe would suppress thalamocortical hyperactivity-induced hyperkinesia as well as influence cognitive and behavioral symptoms (Ligot et al., 2011). To study this effect, the investigators used PET imaging to

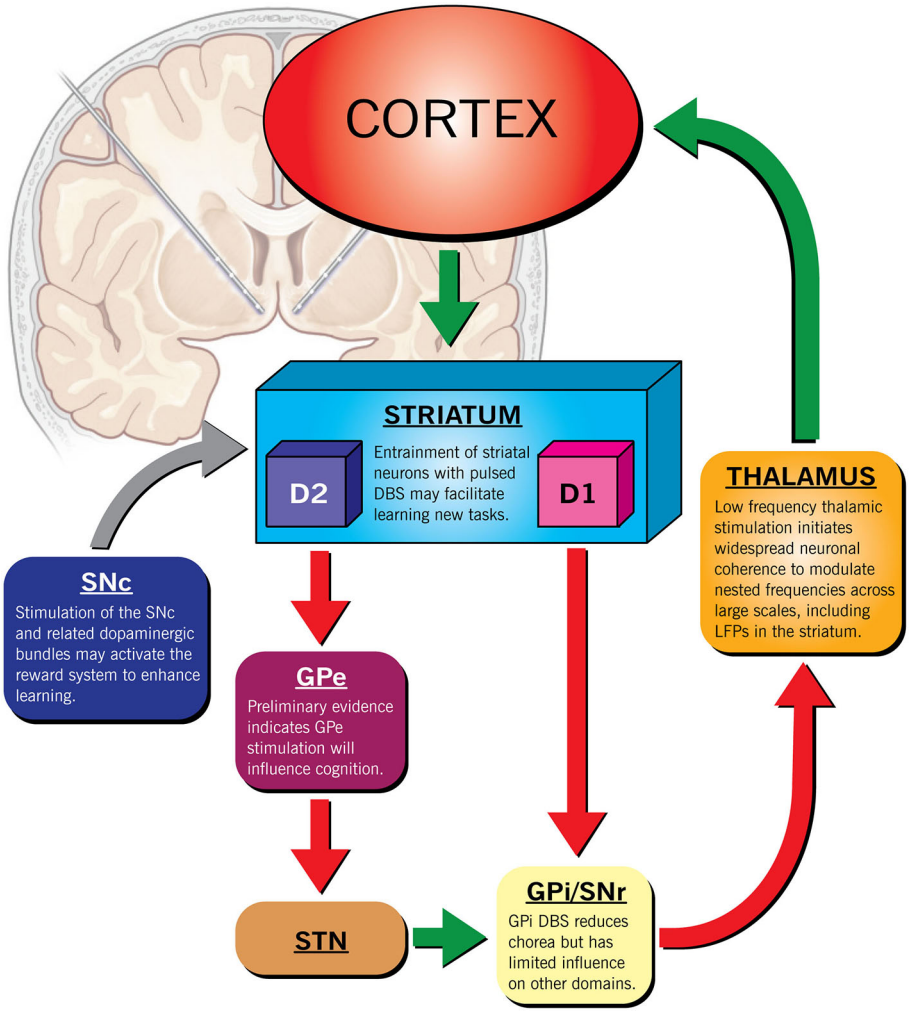

FIGURE 1 | Therapeutic targets for deep brain stimulation in HD. The scale of the response could be modulated by using different stimulation paradigms in addition to the location of the lead(s). For example, increasing dopaminergic activity through SNc stimulation may improve non-specific striatal processing that governs learning. Similarly, thalamic stimulation at low frequencies may modulate multiple nested frequencies simultaneously to re-establish a normal frequency spectrum. High frequency, triggered focal, pulsed stimulation of the striatum paired to a specific task could augment learning of specific skills by boosting event sequencing.

compare 15 control subjects with 5 HD patients implanted with stimulation electrodes in GPe. In the resting state, cortico-subcortical regional cerebral blood flow is reduced in HD with the stimulator off. In keeping with the basal ganglia thalamocortical circuit model, GPe stimulation modulated connectivity and further reduced regional cerebral blood flow in the basal ganglia, cortical structures and the default mode network (Ligot et al., 2011). These findings lead to the conclusion that stimulation of GPe may benefit patients with HD. In a recently completed prospective pilot study, intended to test both GPe and GPi stimulation using a crossover design, DBS of GPe in two patients with HD seemed to restore error processing control, although this effect was washed out when the system was turned off (Beste et al., 2014). Based on these studies and current models of learning, it is our impression, that GPe DBS warrants continued study as a potentially therapeutic target in HD.

Deep Brain Stimulation for HD: Future Directions

The effects of HD lead to cortical disassociation where new behaviors and motor tasks are no longer acquired and existing concatenations that subserve simple and complex skills are decoupled. While the current results of DBS in HD patients may seem disappointing at first, a great deal has been learned. Earlier human studies are primarily aimed at evaluating safety of a novel therapy. The current stage of knowledge seems to support that GPi and GPe DBS may or may not improve motor symptoms but, in general, effects of stimulation were not deleterious. With safety largely established, new studies can be initiated

including controlled trials. New therapies could be aimed at realigning cortical and subcortical structures or reinforce existing pathways, particularly when neural compensation is most responsive (Papoutsi et al., 2014). Cognitive biomarkers that can be detected during the prodromal stages and followed during disease progression, such as working memory, psychomotor speed, reaction to negative emotions, and executive functioning, may be most promising (Dumas et al., 2013).

It is our opinion that DBS may hold promise in preserving brain function in patients with HD to maintain independence and reduce suffering. However, because the phenotypic expression of HD is heterogeneous, DBS may only benefit a select group of patients. Determining this subset is paramount to the success of any intervention. Fortunately, recent large-scale longitudinal studies (such as PREDICT-HD) that have identified specific functional imaging signals indicating early neuronal dysfunction in HD have exposed this window of opportunity. Targeted ES, early in the course of disease may be able to overcome limitations via several mechanisms including: (1) regulation of dopamine homeostasis, (2) focal inhibition or (3) activation of local brain regions, (4) task specific, triggered closed-loop stimulation or (5) diffuse modulation of multiple pathways with low frequency stimulation (**Figure 1**). Deciding when to initiate a disease modifying therapy in HD is challenging. Intervention in the prodromal stage exposes an individual to risk when they may be able to live and work independently for many more years. Similarly, initiating therapy after significant cell death, a precursor to end-stage disease, may be futile. The ethical considerations in delivering neuromodulation should therefore be taken very seriously before such an intervention is delivered to a desperate population (Ford and Kubu, 2006).

The question remains open on whether DBS may have any effect in slowing disease progression in HD. To date DBS has not demonstrated neuroprotection for motor decline in other degenerative conditions (Lilleeng et al., 2014). We believe HD may be unique to PD in the ability to identify gene positive individuals prodromally and closely predict the age of motor symptom onset, early in the course of cortico-striatal dysfunction. Furthermore, even if unable to change the trajectory of a terminal disease such as HD, the ability to successfully improve functional capacity and, in turn, optimism (especially early in the disease process), would have a substantial impact on quality of life at an individual level, and the potential for positive economic consequences at a societal level.

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^{123}I-FP-CIT SPECT imaging in early diagnosis of dementia in patients with and without a vascular component

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Alzheimer's disease (AD) and vascular dementia (VaD) are the most common cause of dementia. Cerebral ischemia is a major risk factor for development of dementia. ^{123}I-FP-CIT SPECT (DaTScan) is a complementary tool in the differential diagnoses of patients with incomplete or uncertain Parkinsonism. Additional application of DaTScan enables the categorization of Parkinsonian disease with dementia (PDD), and its differentiation from pure AD, and may further contribute to change the therapeutic decision. The aim of this study was to analyze the vascular contribution towards dementia and mild cognitive impairment (MCI). We evaluated the utility of DaTScan for the early diagnosis of dementia in patients with and without a clinical vascular component, and the association between neuropsychological function, vascular component and dopaminergic function on DaTScan. One-hundred and five patients with MCI or the initial phases of dementia were studied prospectively. We developed an initial assessment using neurologic examination, blood tests, cognitive function tests, structural neuroimaging and DaTScan. The vascular component was later quantified in two ways: clinically, according to the Framingham Risk Score (FRS) and by structural neuroimaging using Wahlund Scale Total Score (WSTS). Early diagnosis of dementia was associated with an abnormal DaTScan. A significant association was found between a high WSTS and an abnormal DaTScan ($p < 0.01$). Mixed AD was the group with the highest vascular component, followed by the VaD group, while MCI and pure AD showed similar WSTS. No significant associations were found between neuropsychological impairment and DaTScan independently of associated vascular component. DaTScan seems to be a good tool to discriminate, in a first clinical assessment, patients with MCI from those with established dementia. There was bigger general vascular affectation observable in MRI or CT in patients with abnormal dopaminergic uptake seen on DaTScan.

Keywords: dementia, mild cognitive impairment, Framingham risk score, ^{123}I-FP-CIT SPECT

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Introduction

Dementia is a chronic brain syndrome which affects 35.6 million people worldwide and this number is expected to triple by 2050 (115.4 million). Thus, it has an enormous impact on health care provision currently costing the world more than US$ 604 billion per year (Wimo et al., 2013).

The most frequent cause of dementia in the elderly is Alzheimer's disease (AD), followed by vascular dementia (VaD), Parkinson disease with dementia (PDD) and Lewy Body dementia (LBD). Together these account for over 90% of cases of dementia in the elderly (Albanese et al., 2007).

Although they have distinct features, the different types of dementia overlap clinically and pathologically, especially in the early stages and particularly in regards to the contribution of brain ischemia (Iadecola and Gorelick, 2003). Increasing evidence demonstrates that ischemia is not only an additive cause of brain damage in all types of dementia but also contributes specifically to the underlying disease processes (Niwa et al., 2002; Iadecola and Gorelick, 2003) Many cardiovascular risk factors (CVRF), such as hypertension, diabetes, dyslipidemia, and smoking increase the risk of AD, suggesting a vascular contribution to the etiology of AD. Ischemia upregulates and deregulates the entire amyloidogenic cascade. Within the framework of the neurovascular unit, vascular dysfunction may reduce the clearance of β-amyloid (Aβ) via the blood brain barrier or indirectly increase Aβ deposition. Amyloid deposition is considered the pivotal event in the AD pathological cascade, but whether the accumulation is accelerated by CVRF remains unclear (Breteler, 2000; Purnell et al., 2009; **Figure 1**). The evidence is stronger for VaD and AD, but there is a lack of research into the potential contribution of ischemia to LBD or PDD.

Other studies showed that most CVRF also increase the risk for AD (Tatemichi et al., 1994; Tanimukai et al., 1998; Kalaria, 2012). In large epidemiological studies, the prevalence of AD is reported to increase with the severity of atherosclerosis, the presence of atrial fibrillation, hypertension, diabetes mellitus, hyperinsulinemia and insulin resistance, and a previous stroke (Skoog et al., 1996; Leibson et al., 1997; Ott et al., 1997). Antihypertensive treatments can prevent stroke and also the risk of dementia (Sörös et al., 2013). Further, abnormalities in the cerebral white matter thought to be ischemic in nature are more common in AD than controls, and its severity correlates with mild cognitive impairment (MCI) progression to AD (Scheltens et al., 1992; Eckerström et al., 2011).

The occurrence of both AD pathology and vascular brain injury is very common, especially amongst the oldest of old and can be classified as mixed AD. Although epidemiologic studies report that vascular risk factors for arteriosclerosis increase the risk of incident AD, both autopsy, MRI and amyloid positron emission tomography (PET) studies indicate that AD and vascular lesions contribute additively, but independently, to the risk of dementia. The literature confirms the malignancy of AD and highlights the adverse effects of microinfarcts on cognitive function. For the clinical diagnosis of mixed AD, the presence of AD can be recognized by neuropsychological profile, structural imaging, cerebrospinal fluid biomarkers, and glucose PET and amyloid PET imaging. The diagnosis of mixed AD, however, still hinges predominantly on the structural MRI findings (Chui and Ramirez-Gomez, 2015). Studies on neuroimaging have reported that over 70% of patients consulting for neurodegenerative disease have abnormal MRI findings suggestive of a vascular component (Mills et al., 2007). White matter hyperintensities (WMHs) on brain MRI reflect cardiovascular risk profiles, and greater WMH volume is associated with cerebral hypometabolism and cognitive decline, particularly in tests of executive function (DeCarli et al., 1995; Jeerakathil et al., 2004; Carmichael et al., 2010). These structural and cognitive changes were associated with CVRF. The Framingham Stroke Risk Profile score, a composite risk score of CVRF that measures 10-year probability of stroke, was negatively associated with total cerebral brain volume and positively related to prevalent WMHs. The association between multiple CVRF was examined by a number of studies using the Framingham Stroke Risk Profile. High Framingham scores correlate with poor cognitive performance (Wolf et al., 1991; Elias et al., 2004; Jeerakathil et al., 2004). These results confirm that ischemia is a major risk factor for dementia. In fact, 10% of stroke patients develop dementia shortly after their first stroke and more than a third develop dementia after recurrent strokes. Subjects not developing dementia as a direct consequence of a stroke have a 10-fold increase in the risk of dementia over the next 5 years (Pendlebury and Rothwell, 2009).

Neuroimaging techniques play a major role as diagnostic instruments (Visser et al., 2012). In particular, emission tomography (single photon emission computed tomography, SPECT and PET) provides a unique tool to investigate functional and neurochemical changes, both in those with established dementia and at risk of subsequent cognitive decline (de Souza et al., 2012; Herholz, 2012).

AD is characterized by bilateral temporoparietal hypoperfusion on SPECT and hypometabolism on PET, which may precede the onset of clinical dementia. Similar changes can be demonstrated in those with MCI and in those genetically at risk of developing AD (Brun and Englund, 1986; Vanitallie, 2013). In turn, VaD is related to multiple, asymmetric, perfusion deficits secondary to brain multi infarction (Chen et al., 2013).

In contrast, in LBD medial parietal and occipital perfusion deficits are seen together with mainly pre-synaptic dopaminergic changes, most commonly a reduction in the striatal pre-synaptic dopamine transporter (DAT) which can be visualized using appropriate tracers [e.g., ^{123}I-N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane (^{123}I-FP-CIT SPECT); McKeith et al., 2005; Cummings et al., 2011].

Thus, advanced functional imaging has a promising potential in supporting dementia diagnosis. Indeed, imaging of the DAT defines integrity of the dopaminergic system, and hence its degeneration *in vivo* (Varrone and Halldin, 2010). Its main clinical application is in patients with mild, incomplete, or uncertain Parkinsonism (Weng et al., 2004; Tolosa et al., 2007; Eshuis et al., 2006). That is, striatal uptake correlating with

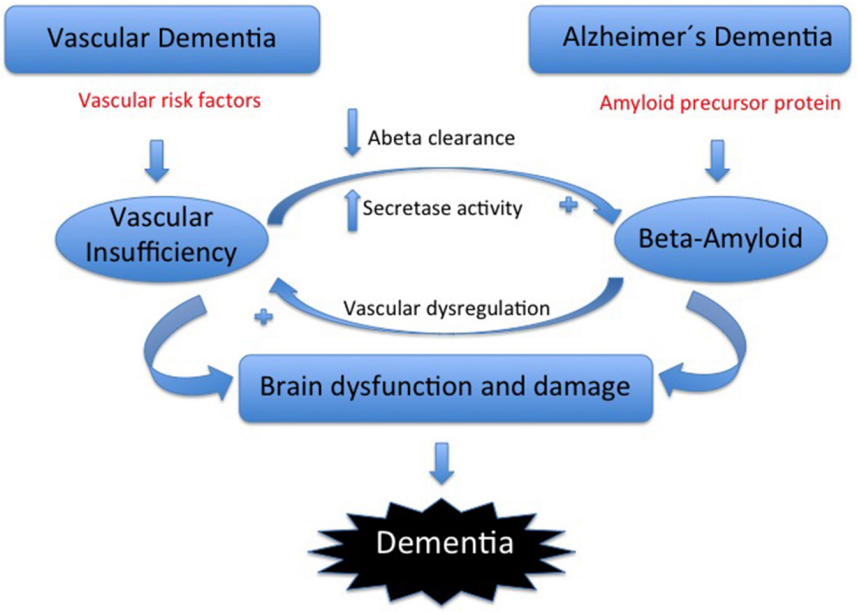

FIGURE 1 | In VaD, cerebrovascular risk factors induce neurovascular dysfunction leading to brain dysfunction and damage. In Alzheimer's disease (AD), cleavage of amyloid precursor protein by by β- and γ-secretases leads to Aβ accumulation, which also causes brain dysfunction and damage. Although individually these pathways are capable of inducing cognitive impairment, their interaction enhances their pathogenic effects. Thus, Aβ induces vascular dysregulation and aggravates vascular insufficiency, thereby enhancing the brain dysfunction and damage associated with vascular risk factors. In addition, the hypoxia-ischemia resulting from the vascular insufficiency increases Aβ cleavage from APP and reduces Aβ clearance through the cerebral vasculature, promoting Aβ accumulation and the attendant deleterious effects on the brain (Iadecola, 2010).

disease severity, in particular bradykinesia and rigidity. Also, it is a useful tool in the monitoring of progression in clinical trials of potential neuroprotective drugs and in differentiating juvenile-onset Parkinson's disease (abnormal ^{123}I-FP-CIT SPECT) from dopa-responsive dystonia (normal ^{123}I-FP-CIT SPECT; Marshall and Grosset, 2003).

Dopamine loss is seen even in the earliest clinical presentations of true Parkinsonism; a normal scan suggests an alternative diagnosis such as essential tremor, drug-induced Parkinsonism, or psychogenic Parkinsonism (Cummings et al., 2011). Congruence between working clinical diagnosis and DAT imaging increases over time in favor of baseline ^{123}I-FP-CIT SPECT imaging results. Additional applications, especially accurate when combining with other neuroimaging tools such as FDG-PET, characterize dementia with Parkinsonian features (Cummings et al., 2011; Garibotto et al., 2013). Furthermore, it is possible to differentiate AD from LBD [normal tracer uptake in AD and abnormal in dementia with Lewy bodies (DLB) with sensitivity and specificity of 78−88% and 94−100%, respectively; McKeith et al., 2005].

Regarding the vascular component involved in dementia, the role of nuclear medicine imaging in the diagnosis of vascular Parkinsonism (VP) or VaD has been addressed by only a few studies up to now and with non-definitive results. Some of these suggest normal ^{123}I-FP-CIT SPECT (Gerschlager et al., 2002; Lorberboym et al., 2004; García Vicente et al., 2005) in VP while others suggest reduced ^{123}I-FP-CIT binding as well as a lower mean asymmetry index than Parkinson's disease (Zijlmans et al., 2007). In general more studies reported higher percentage of normal FP-CIT SPECT in VP patients (Bouwmans et al., 2013).

The aim of this study was to analyze the vascular contribution towards dementia and MCI. We evaluated the utility of FP-CIT SPECT for the early diagnosis of dementia in patients with and without a clinical vascular component, and the association between neuropsychological function, vascular component and dopaminergic function on FP-CIT SPECT.

Materials and Methods

Subjects

The study population included 105 patients. They were recruited prospectively from the outpatient Dementia and Stroke Unit. We included patients with clinical diagnosis of MCI (n = 50), probable dementia (AD and VaD, n = 37), and Parkinson disease with dementia (PDD and DLB, n = 18; **Table 1**).

TABLE 1 | Distribution of different diagnoses in our study group.

	N	Age	Sex M:F
Mild cognitive impairment (MCI)	50	72 ± 8	26:24
Alzheimer's disease (AD)	31	76 ± 7	12:19
Parkinson disease with dementia (PDD)	12	77 ± 6	10:2
Vascular dementia (VaD)	6	73 ± 9	3:3
Lewy body dementia (LBD)	6	73 ± 11	3:3

Data are presented as mean (±SD) or number.

Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), and AD based on the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke* and the *Alzheimer's Disease and Related Disorders Association* for definite, probable, or possible. Independently, two trained neurologists made the diagnosis and the final diagnosis was established by consensus. Patients with hemispheric vascular accident or severe isolated aphasia were not included. Also, patients with prior cranial trauma, severe heart, kidney or liver disease, cancer or infection signs were excluded from our study.

Baseline Assessment

Demographic and Clinical Variables and Cardiovascular Risk Profile

Demographic data included age and gender. We also recorded medical history including data such as CVRF and psychiatric disorders. CVRF were extracted from the medical history: hypertension, dyslipidemia, Diabetes Mellitus, smoke habit, family history of dementia or cardiovascular disease, presence of peripheral vascular disease (PVD), coronary artery disease (CAD) or prior stroke. Cardiovascular risk score was calculated using the recently developed Framingham General Cardiovascular Disease Risk from the Framingham Heart Study (Wolf et al., 1991; D'Agostino et al., 2008). Framingham Risk Score (FRS) was estimated in all patients according to age, gender, total cholesterol levels, HDL levels, systolic blood pressure, hypertension treatment, smoking habit, diabetic status, and vascular disease (CAD, PVD, stroke). Those patients presenting moderate or high FRS were categorized as having a clinical vascular component, while all the rest were considered as not having it.

Data were provided by the patient and/or caregiver or extracted from medical reports if available.

Physical Examination

Neurological clinical examination was performed. Assessments were undertaken according to the local practice. The Mini-Mental State Examination (MMSE) was administered as a cognitive screening test. The effect of cognitive impairment on global functioning was measured with the Clinical Dementia Rating Scale (CDR) and the Global Deterioration Scale (GDS). Instrumental activities of daily living (IADL) and ADL functions were measured with the Blessed Dementia Rating Scale (BDRS), the Bayer ADL or self-rating Bayer ADL scale.

Motor sub-scale of the Unified Parkinson's Disease Rating (UPDRS- III) was used as a measure to help in the description of the extrapyramidal symptoms (EPS). Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI) and depression rates on the elderly were measured with the Yesavage scale.

Neuropsychological Battery

A standardized protocol was administered by a trained neuropsychologist. We selected a short version of the Barcelona test. The domains tested were orientation, attention, immediate and differed memory, language, praxis, gnosis, executive functions and working memory. Neuropsychologists were also asked to give a GDS of the cognitive impairment evaluated.

Complementary Physical Examinations

General blood tests were realized including lipid profile. According to our laboratory criteria, lipid abnormal profile was defined as cholesterol levels higher than 200 mg/dl, high density lipoprotein cholesterol (HDL) lower than 56 mg/dL if men and lower than 65 mg/dL if women, low density lipoprotein (LDL) cholesterol higher than 100 mg/dl and triglycerides higher than 190 mg/dL.

Neuroimaging Study

In addition to the clinical vascular component defined using FRS, the vascular contribution in each group of patients was also quantified from WMHs on anatomic neuroimaging.

MRI and CT imaging

MRI was used preferentially, if not available CT was used. MRI was performed on a Symphony MR A-35 1.5 T scanner and processed using MR 2004 A Syngo software. CT imaging was performed on Siemens Sensation Somaton E scanner and processed using the software CT 2007 –S 16 C. Axial CT or T2 weighted MRI images were used for the quantification of the vascular component using a validated score according to Wahlund scale (from 0 to 3; Wahlund et al., 2001). The Wahlund scale was used in the analyses of WMHs in five cerebral areas in both hemispheres: frontal, parieto-occipital, temporal lobes, infratentorial area and basal ganglia. WMHs on MRI were defined as ill-defined hyperintensities >5 mm on T2 images, and on CT as ill-defined and moderately hypodense areas of >5 mm. Lacunes were described as well-defined areas of >2 mm with attenuation (on CT) or signal characteristics (on MRI) the same as cerebrospinal fluid. If lesions with these characteristics were <2 mm, they were considered perivascular spaces. Changes in the basal ganglia were rated in the same way and considered WMHs even if located in the gray matter nuclei, which contains a small amount of white matter. The Total Score of the Wahlund Scale (WSTS) was finally quantified as the mean value of the five cerebral areas analyzed.

Molecular imaging of dopaminergic activity by [123]I-FP-CIT SPECT

SPECT images were acquired on a 2 headed gamma camera hybrid SPECT-TC Infinia HW4 General Electronic with a high resolution collimator. Images were acquired 3 h after a single intravenous injection of 5 mCi (111–185 MBq) of the radiotracer ^{123}I Ioflupane. Subjects underwent standard thyroid blocking with potassium iodide oral administration (120 mg) 1–4 h before and 12–24 h after the radiotracer injection. Images were assessed using a dichotomous division of normal (0) *vs.* lower uptake (1).

Statistical Analyses

Demographic parameters were expressed as absolute values and percentages for the qualitative variables and by mean and standard deviation for the quantitative variables.

In bivariate analysis, qualitative variables were compared using the χ^2 test or Fisher exact probability Test, when appropriated. To complete the comparison between qualitative and quantitative variables Student's *t*-test was carried out. For the mean comparisons ANOVA test was used. Finally, Pearson correlation coefficients were used to examine the relationship between quantitative variables. A two-sided *P* value of <0.05 was used to assess statistical significance. For significant variables, 95% confidence intervals (CI) were established.

Statistical analyses were performed using the Statistical Package for the Social Sciences SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Ethical Considerations

This study was done in accordance with the Review Board and Ethics Committee of our center. Written informed consent was always obtained from patients.

Results

Subject Demographics

Subject's demographic characteristics, CVRF, results of neurological, neuropsychological and neuroimaging examination frequencies of MCI group compared to the dementia group are shown in **Table 2**. In **Table 3** the same features are described as N(%) for each dementia type and also MCI.

Vascular History and Risk Factors

Within clinically diagnosed AD, 7 out of 31 patients had vascular lesions on imaging and were classified as mixed AD. However, none of the CVRF studied was associated with dementia. Similar frequencies of hypertension were seen in MCI and dementia (62 *vs.* 66%, respectively). The same smoking habit frequency was found in MCI compared to dementia (21%). Zero percent smokers were found in the VaD group and the highest frequency existed in DLB (40% smokers).

HDL levels were normal for all the different subtypes of dementia except DLB and PDD, which presented with lower levels (36 ± 22 mg/dL and 47 ± 13 mg/dL, respectively). Elevated LDL levels were found in AD (136 ± 48 mg/dL). Overall dementia presented with general abnormal triglycerides levels (171 ± 59 mg/dL).

Regarding the clinical component according to FRS, no significant association was found with dementia compared to MCI (frequencies of 64% and 63%, respectively). When studying the different types of cognitive impairment separately, PDD showed the highest frequency (92%) followed by VaD (67%), MCI (63%), DLB (60%) and AD (53.6%).

Related to the presence of PVD this showed the highest frequency within the VaD group (20%) and no significant differences were observed between MCI (5%) and overall dementia (7%). The dementia group presented with higher frequency (14 *vs.* 10% in MCI) of CAD, and similar frequencies were seen in AD, VaD, PDD (13, 20 and 22% respectively). MCI patients had more prior strokes than dementia patients (37 *vs.* 26%). When ischemic lesions were examined according to Hachinski ischemic scale, VaD had the highest score (6 ± 5 total score).

TABLE 2 | Subject's demographic characteristics, distributions of CVRF, results of neurological, neuropsychological and neuroimaging examination in MCI group compared to the dementia group.

N (%)	MCI	Dementia
Sex M:F	26 (52):24 (48)	29 (53):26 (47)
Age	72 ± 8	75 ± 8
Vascular component	14 (29)	14 (26)
EPS	0 (0)	17 (31)
Hypertension	29 (62)	31 (66)
Dyslipidemia	16 (34)	17 (36)
Diabetes mellitus	12 (26)	15 (32)
Smoking or ex-smoking	10 (21)	10 (21)
PVD	2 (5)	3 (7)
CAD	4 (10)	6 (14)
Prior stroke	15 (37)	11 (26)
Total cholesterol	194 ± 40	190 ± 47
HDL cholesterol	50 ± 18	51 ± 21
LDL cholesterol	108 ± 63	103 ± 55
Triglycerides$^{\sharp}$	137 ± 100	171 ± 59
HACHINSKI	4 ± 3	4 ± 3
GDS *fast*	3 ± 1	4 ± 1
MMSE$^{\sharp}$	25 ± 4	21 ± 5
UPDRS-III *motorsub-scale*$^{\sharp}$	9 ± 9	37 ± 15*
WSTS$^{\sharp}$	0.5 ± 0.4	0.7 ± 0.6
^{123}I-FP-CIT SPECT decrease uptake$^{\sharp}$	7 (21)	14 (45)

*Numbers and % are presented for each group. $^{\sharp}p < 0.05$; *This refers only to PDD group.*

Parkinsonism Features

The presence of extrapyramidal signs (EPS) was measured with UPDRS III (motor subscale) test. In our sample, 17 patients presented with EPS, corresponding to all patients with PDD and DLB. UPDRS III scores were higher in PDD than in MCI (mean values of 37 *vs.* 9 in a 0–108 scale).

Cognitive Test Function and Neuropsychological Battery

Our population of probable dementia patients did not show significant differences regarding MMSE scores among dementia subtypes (mean MMSE score for probable dementia and MCI was 21 and 25, respectively).

A significant association was found between dementia and the global neuropsychological function, measured as a summary of the different affected areas ($p = 0.025$).

When we analyzed each neuropsychological area separately, patients with overall dementia (regardless of dementia subtype) had a higher frequency of affectation of the orientation domain compared to those with MCI (35% in MCI and 58% in dementia,

TABLE 3 | Subject's demographic characteristics, CVRF, results of neurological, neuropsychological and neuroimaging examination in different dementia subtypes and in MCI patients.

N (%)	AD	VaD	PDD	LBD	MCI
Vascular component	7 (23)	5 (83)	2 (17)	0	14 (28)
EPS	0	0	12 (100)	6 (100)	0 (0)
Hypertension	18 (67)	4 (80)	8 (80)	1 (17)	29 (62)
Dyslipidaemia	9 (33)	2 (40)	4 (40)	2 (33)	16 (34)
Diabetes mellitus	6 (22)	2 (40)	4 (40)	3 (50)	12 (26)
Smoking or ex-smoker	6 (22)	0	2 (20)	2 (33)	10 (21)
PVD	1 (4)	1 (20)	1 (11)	0	2 (5)
CAD	3 (13)	1 (20)	2 (22)	0	4 (10)
Prior stroke	5 (21)	3 (60)	2 (22)	1 (17)	15 (37)
Total cholesterol	205 ± 49	165 ± 39	172 ± 34	186 ± 62	194 ± 4
HDL cholesterol	56 ± 17	66 ± 30	36 ± 22	47 ± 14	50 ± 18
LDL cholesterol	136 ± 48	83 ± 22	82 ± 56	74	108 ± 63
Triglycerides	144 ± 65	84 ± 31	97 ± 46	117 ± 68	137 ± 100
HACHINSKI	4 ± 3	6 ± 5	5 ± 3	2 ± 2	4 ± 4
GDS *fast*	4 ± 1	NA	4 ± 1	NA	3 ± 1
MMSE	22 ± 5	22 ± 6	19 ± 3	19 ± 6	25 ± 4
UPDRS-III *motor sub-scale*	NA	NA	38 ± 17	33 ± 4	9 ± 9
WSTS	0.6 ± 0.5	0.7 ± 0.6	0.8 ± 0.5	0.3 ± 0.4	0.5 ± 0.4
^{123}I-FP-CIT SPECT lower uptake	3 (23)	0 (0)	7 (78)	4 (80)	7 (21)

Numbers and percentage are presented.

$p < 0.05$). Speech was also more affected in dementia (16% in MCI and 39% in dementia, $p < 0.05$) and gnosis alterations was not found in MCI (0%) while 13% of patients with dementia presented with gnosis alterations ($p < 0.05$). No significant differences were found in relation to the other tested functions (memory, working memory, attention, praxis).

Association Between Vascular Component and WSTS

We used the WSTS to quantify the vascular lesions observed either in MRI or CT and then studied their association with the qualitatively established clinical vascular component.

An association was found between the presenting clinical vascular component according to FRS and WSTS calculated using MRI and CT images. Patients presenting with a clinical vascular component showed a higher mean WSTS (mean WSTS 0.7 *vs.* 0.4, $p < 0.05$ respectively).

We also found significant association regarding frontal, basal ganglia, infratentorial and Wahlund Scores with vascular component according to FRS ($p < 0.05$).

Association Between WSTS and Clinical Diagnoses: Mixed AD has Higher WSTS than Other Dementia Types or MCI

One of our aims was to study the contribution of the clinical vascular component towards brain damage and dementia. Hence, after seeing association between clinical vascular component according to FRS and WSTS, we wanted to look at the association between having a high WSTS and the clinical diagnoses of either dementia or MCI. Although not being statistically significant, the highest mean WSTS was found in the PDD group of patients. Moreover, when AD patients with clinical vascular component (mixed AD, 7/31 patients) were separated from the pure AD they appeared to have the highest WSTS. In contrary, pure AD showed a lower WSTS, even lower than that observed in MCI (**Figure 2**).

Association between area-specific WSTS and clinical diagnosis was only found in infratentorial WSTS, which is linked to PDD ($p < 0.05$).

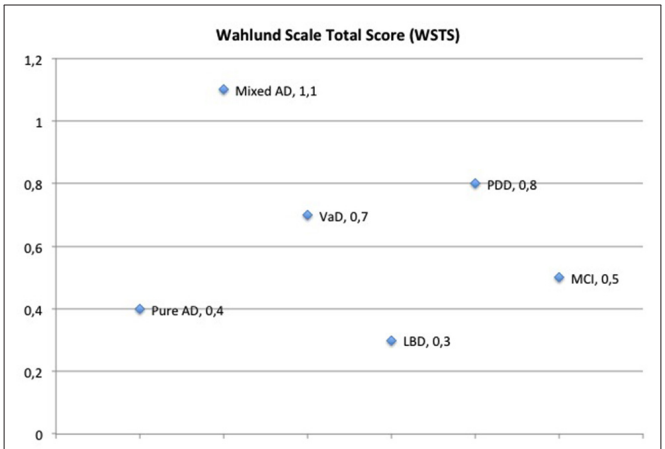

FIGURE 2 | Mean values of wahlund scale total score (WSTS) measured on MRI/CT for each patient group. AD patients with clinical vascular component (mixed AD) have the highest score, followed by VaD and PDD. DLB showed the lowest score, while mild cognitive impairment (MCI) and pure AD presented with comparable values.

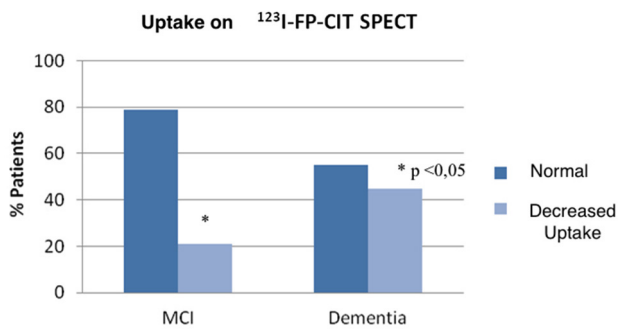

FIGURE 3 | Dopaminergic uptake distribution observed on ^{123}I-FP-CIT SPECT for MCI and dementia group.

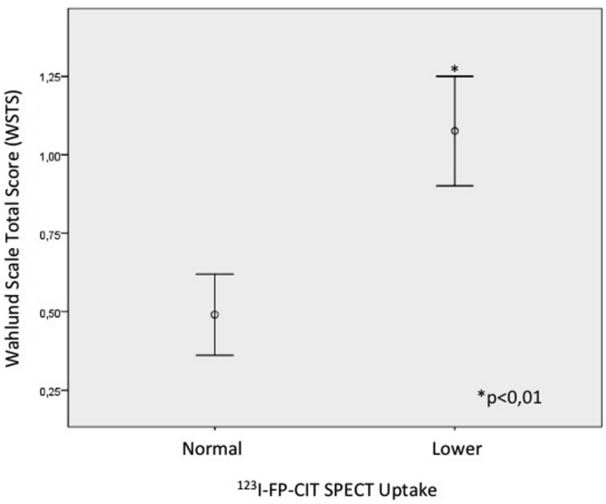

FIGURE 4 | Association between WSTS and abnormal dopaminergic uptake in ^{123}I-FP-CIT SPECT ($p < 0.01$).

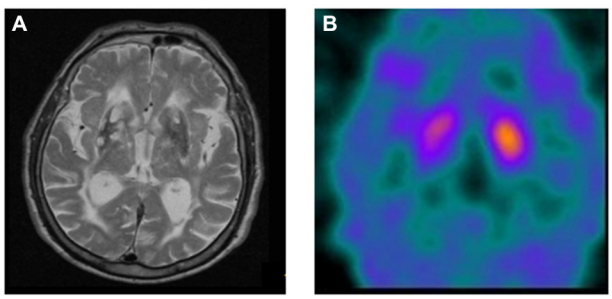

FIGURE 5 | MRI and ^{123}I-FP-CIT SPECT Images from a representative patient to show relation existing between abnormal MRI and uptake on ^{123}I-FP-CIT SPECT. (A) MRI T2-potentiated showing diffuse cerebral atrophy with increased size and depth of cerebral grooves and ventricular supratentorial enlargement. Multiple lacunar chronic infarctions, some of those were hemeorrhagic in the lenticular and head of caudate nuclei. Chronic periventricular ischemia leucoencephalopaty and focal hyperintensities in parietal frontal and temporal bilateral white matter WSTS = 1.6. **(B)** ^{123}I-FP-CIT SPECT from the same subject showing detectable decreased uptake in right putamen.

Association Between Clinical Diagnoses and Uptake in ^{123}I-FP-CIT SPECT

^{123}I-FP-CIT SPECT was available in 33 MCI and 31 dementia patients (13/31 AD, 4/6 VaD, 9/12 PDD, 5/6 LBD, respectively), a total of 61% of studied population. A significantly higher frequency of decreased uptake in ^{123}I-FP-CIT SPECT was found in patients with dementia compared to MCI (21% patients with decreased uptake in MCI *vs.* 45% patients in dementia group, $p < 0.05$; **Figure 3**; **Table 2**). As expected, patients with Parkinsonism (DLB and PDD) showed the highest frequency of decreased dopaminergic uptake (80% in DLB and 78% in PDD; **Table 3**).

Association Between WSTS and Dopaminergic Uptake in ^{123}I-FP-CIT SPECT

A significant association was found between dopaminergic uptake seen on ^{123}I-FP-CIT SPECT and the vascular component quantified using WSTS ($p < 0.01$; **Figure 4**). Thus, patients presenting higher WSTS more frequently showed an abnormal ^{123}I-FP-CIT SPECT image ($p < 0.01$; **Figure 5**).

Nevertheless, no significant association was found between an abnormal ^{123}I-FP CIT SPECT image and the vascular component according to FRS.

No Association Between Dopaminergic Uptake ^{123}I-FP-CIT SPECT nor WSTS and Neuropsychological Function

In relation to the association between dopaminergic uptake observed in ^{123}I-FP-CIT SPECT and the neuropsychological function examined by an ordinary test battery. No significant results have been obtained when studying each neusopsychological function separately, and neither with the overall performance on neuropsycological tests. No relationship was found between neuropsychological function and the clinical vascular component measured using WSTS.

Discussion

In this study we aimed to analyze the contribution of vascular component (assessed clinically and on neuroimaging) to clinical diagnoses of the common types of dementia and MCI. We tested the potential application of ^{123}I-CIT-SPECT imaging in dementia, particularly when the vascular component is present. We looked at the association between having vascular component and presenting an abnormal ^{123}I-CIT-SPECT. Finally, we studied the association between neuropsychological function and vascular component or abnormal ^{123}I-CIT-SPECT. A better understanding of the association between these variables could help providing new tools for a more accurate and early diagnoses of common types of dementia.

Our results showed an association between clinical vascular component according to FRS and quantification of the vascular component using WSTS on MRI and CT images. These results are in line with what would be expected and confirm the reliability of the quantification of WMHs lesions using Wahlund scale in our population (Wahlund et al., 2001). Further, it confirms that it was a well selected population. The association

between WMHs for each brain area separately was significantly different in frontal, basal ganglia and infratentorial areas. However, no association was found within the temporal area, which actually would be the most likely, considering that most frequent types of AD-like dementia are characterized by temporo-parietal alterations (Fischer et al., 1990; Jabłoński et al., 2011; Marchesi, 2011).

It was observed in previous studies that vascular lesions contribute to cognitive decline. It was suggested that cerebrovascular lesions induce amyloid deposition perhaps accelerating the process of dementia (Garcia-Alloza et al., 2011; Pluta et al., 2013). Although, we did not find a significant association between the different clinical diagnoses of cognitive impairment and WSTS, we have observed a notable frequency of the vascular component on neuroimaging within the AD group. The later group probably was formed by mixed AD population. These findings confirmed the fact that vascular accident history contributes to the etiology and/or progression of dementia. Patients with mixed AD and PDD had a high WSTS, even higher than in patients with VaD. Although not being statistically significant, these results are in line with the association between AD or PDD and WMHs. No conclusions can be drawn related to overall dementia and MCI WSTS.

In relation to the particular areas affected by ischemic lesions and each diagnoses, we only found a significant association relating to the infratentorial region in PDD. This could be explained by the fact that in our PDD group there was a high frequency of VP, as this group presented with a high mean of WSTS (0.8 ± 0.5) with 92% frequency of clinical vascular component according to FRS. Further, the non-association of VaD and any specific brain region could be due to a diffuse pattern of this type of dementia, unusual low FRS of this group and/or the few number of patients in this group.

Furthermore, we evaluated the potential utility of ^{123}I-FP-CIT SPECT as a diagnostic tool to discriminate dementia from MCI, and differentiate among different dementia types, emphasizing on dementia with a vascular component. Our study showed that ^{123}I-FP-CIT SPECT is a useful tool to discriminate MCI from overall dementia subtypes. This is a promising observation, since it is a major clinical priority to be able to more accurately confirm dementia diagnoses and predict MCI progression. However, in our study we could not demonstrate the utility of ^{123}I-FP-CIT SPECT to discriminate among different dementia types.

As expected, most of patients with PDD and all but one of those with LBD showed an abnormal ^{123}I-FP-CIT SPECT. Nevertheless, three patients with PD did not show an abnormal ^{123}I-FP-CIT SPECT, suggestive of possible iatrogenic Parkinsonism. We hypothesized that patients with VaD could show an abnormal ^{123}I-FP-CIT SPECT if ischemic lesions affected directly or indirectly the dopaminergic control of cortical-striatal circuits. This was not seen in our study probably because of the small number of patients with VaD ($n = 6$), none of which showed abnormal ^{123}I-FP-CIT SPECT.

Once we had demonstrated the utility of ^{123}I-FP-CIT SPECT to differentiate dementia *vs.* MCI, we then studied the association between abnormal ^{123}I-FP-CIT SPECT and presence of the vascular component clinically assessed with the FRS and quantified on neuroimaging using WSTS. An association between the vascular component according to FRS and abnormal ^{123}I-FP-CIT SPECT was not found, but the association between dopaminergic function and WSTS was statistically significant. Thus, our results showed that ^{123}I-FP-CIT SPECT discriminates between vascular risk factors load and vascular component quantified using WSTS and that neuroimaging of vascular lesions is indeed important. Wahlund scale criteria thus being more accurate in analysing the grade of vascular component observable than classical FRS. It is interesting that WSTS, as a global brain WMHs score, rather than basal ganglia sub-score, is associated with an abnormal ^{123}I-FP-CIT SPECT imaging. This suggests that this technique can reflect vascular alterations other than those affecting basal ganglia. The association observed between abnormal ^{123}I-FP-CIT SPECT and the vascular component quantified by WSTS could be justified because dementia patients have a significantly higher frequency of abnormal ^{123}I-FP-CIT SPECT, in particular, the PDD group seems to be the responsible for this finding. PDD and LBD had the highest frequency of abnormal ^{123}I-FP-CIT SPECT and PDD showed the second highest WSTS after mixed AD. Moreover, AD showed a high vascular contribution (high mean WSTS) and the frequency of abnormal ^{123}I-FP-CIT SPECT was higher (23%) than expected according to previous reports that confirm the utility of ^{123}I-FP-CIT SPECT in the differentiation of PDD/LBD from AD (O'Brien et al., 2009; Cummings et al., 2011). Some studies reported that approximately 5–10% of ^{123}I-FP-CIT SPECT in patients with clinical dementia showed intermediate scans. Thus, abnormal images within AD group may represent mixed LBD/AD disease (Kemp and Holmes, 2007).

In conclusion, our study supports the utility of ^{123}I-FP-CIT SPECT to detect abnormal dopaminergic function in those patients that showed a high WSTS corresponding to a high grade of generalized ischemic brain lesions. This decrease uptake could be due to the loss of dopaminergic innervation in the striatum as a consequence of ischemia or the alteration of dopaminergic system because of abnormal cell functionality, characteristic of oxidative stress that could precede cell death in dementia or MCI (Kim et al., 2012).

There is growing evidence demonstrating that the vascular component has an active role in dementia mechanisms and its progress and is probably involved in most dementia subtypes which share similar physiopathological features (Iadecola and Gorelick, 2003). Therefore, it is not surprising that an abnormal ^{123}I-FP-CIT SPECT is associated with cerebrovascular lesions related to dementia, but cannot differentiate among dementia subtypes that have an important vascular component, such as mixed AD, VaD or VP.

It is known that ^{123}I-FP-CIT SPECT is useful to discriminate AD from PDD/LBD, and hence to distinguish patients in whom dopaminergic therapy may be beneficial (Varrone and Halldin, 2010; Cummings et al., 2011). Therefore, an abnormal

scan suggests underlying neurodegeneration, supportive of a diagnosis of Parkinson's disease, or atypical parkinsonism, LBD and even VP if the nigrostriatal system is affected. Conversely, a normal dopaminergic imaging supports an alternative diagnosis such as AD, essential tremor or iatrogenic parkinsonism. In our study, we demonstrated that ^{123}I-FP-CIT SPECT could be also useful to confirm diagnosis of dementia among those patients with MCI.

Recent studies have demonstrated a 6–8% decline of DAT per decade (Erixon-Lindroth et al., 2005), suggesting DAT binding is a powerful mediator of age-related cognitive changes. These findings should be taken under consideration when designing and interpreting *in vivo* imaging studies.

Finally, this study did not find a significant association between neuropsychological function and abnormal ^{123}I-FP-CIT SPECT nor high WSTS. This suggests that neither measurement of vascular component score nor the functionality of dopaminergic system can detect degree of cognitive decline in our sample.

Limitations

It is important to note that patients with VaD in our sample had lower FRS scores than expected; the distribution of CVRF was low and they did not appear to have the highest WSTS-being lower than those observed in AD, where cholesterol levels seemed to be a risk factor to develop AD. This fact could be due to the small number of patients in our sample, especially in the VaD group. Another limitation of our study was the use of clinical diagnosis as the gold standard, which may not always be accurate.

Further studies are needed to better elucidate the potential role of dopaminergic transporter imaging on detecting vascular brain damage and its association with clinical dementia.

Conclusion

In agreement with previous reports ^{123}I-FP-CIT SPECT imaging is abnormal in patients with extrapyramidal signs (PDD and DLB). Interestingly, around 20% of patients with pure AD or MCI had abnormal SPECT. The new finding is that on initial visit ^{123}I-FP-CIT SPECT can differentiate severity in terms of classification between MCI and dementia, thus helping establish more accurately initial diagnosis and maybe providing a useful tool to discriminate MCI from overall dementia at clinical practice. Furthermore, in our sample, the vascular contribution is shown to be relevant and present among AD and PDD patients, in line with previously reported data and in addition, there is a good correlation between uptake on ^{123}I-FP-CIT SPECT and ischemic score on MRI or CT.

Author Contributions

All authors contributed to work. Marta Milà and Marina Garriga participated in patients selection, screening and follow up. Manzoor Mir and Raid Al-Baradie helped with analysis of data, Sonia Huertas, Cesar Castejon, Miguel Aguilar, Jerzy Krupinski evaluated patients, helped with manuscript, Laura Casas and Dolors Badenes performed neuropsychological tests. Marta Milà, Raid Al-Baradie, Manzoor Mir analyzed molecular images, Marta Milà and Marina Garriga quantified MRIs. All authors contributed to the final version of the manuscript.

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Enhancing cognition before clinical symptoms of dementia

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As the title of the special issue indicates, controversy surrounds augmentation of brain cognition in humans. Lacking efficacious drugs for Alzheimer's disease (AD) and with many AD patients recruited for clinical trials that unfortunately do not provide the expected results, one wonders whether to test cognition enhancement strategies in individuals without symptoms of cognition decline. This opinion article presents the view that safe drugs and or dietary supplements should be tested worldwide in aged individuals under the control of a non-for-profit organization.

Unfortunately, the effort to translate the results in rodents into patients with dementia, mainly of the Alzheimer's type has not provided the expected results. The reasons for the loss-in-translation are varied (see Franco and Cedazo-Minguez, 2014). Moreover, failures on achieving efficacious anti-AD medications and the high cost of performing clinical trials make pharmaceutical companies to abandon the dementia field (see http://www.abc.net.au/pm/content/2012/s3611062.htm). Clinical trials face the difficulty of patient recruitment and the need—due to ethical reasons- to maintain the already approved anti-AD medication. It is difficult to attain the primary outcomes in AD patients under a multi-drug treatment regime. An alternative approach consists of testing cognition enhancement in individuals not taking anti-AD medication, even in those without any clinical symptom of dementia.

A controversy concerning supplements of vitamin D in individuals with little or no clinically-relevant symptoms attracted enough interest to allocate one discussion session in the 15th European Congress of Endocrinology held in Copenhagen in 2013. A similar controversy on testosterone supplementation exists among endocrinologists and nutritionists. Solid reasons emerge for and against the convenience of those supplementations; yet these compounds are easily available. On analyzing the benefit-risk balance, the main concern is the side effects that may appear after chronic treatment with vitamin D or testosterone. A similar concern arises on thinking about the possibility to prescribe cognition enhancers under a chronically regime. Research in animal models clearly indicates that cognition enhancement is possible. Should drugs with cognition-enhancing potential in mice models of dementia be tested in healthy humans? I consider, for instance, that safe drugs deserve a chance to be tested in aged non-demented humans.

Relevant for the present discussion is that drugs may be prescribed to individuals without any clinical symptom. Statins, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are instrumental for the prevention of cardiovascular dysfunction in hypercholesterolemic patients. Statins are taken in familial hypercholesterolemia at relatively high doses, chronically and from very early in life. Statins are safe as deduced from the records of millions of patients taken the medication since 1985, when the first statin was available for human use. Statin development was on the verge to be abandoned due to potential side effects of blood lipid-lowering drugs. An important pharmaceutical company took the decision of discontinuing statin development. Relevant here is that the "*FDA*—food and drug administration—*became actively involved in maintaining interest in the development of the statins.*" Also relevant is that "*there was no proof at that time*—early eighties—*that drugs or diet used to lower cholesterol would be the clinical equivalent of patients with spontaneously occurring low cholesterol*," meaning that statins were being developed without the certainty that lowering cholesterol by statins could be efficacious in combating atherosclerosis. The full drug development story is available at http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm082054.htm. In summary, safe and efficacious statins are prescribed even in the absence of clinical symptoms.

Interestingly, some compounds approved for non-CNS indications have shown cognition enhancing properties in animal models of AD. As scientist in a laboratory on translational AD research I had experience on two drugs with good safety records: 4-phenylbutyrate (PBA) and tadalafil. The first is used in children with thalassemia, sickle-cell disease or congenital defects in enzymes of the urea cycle (Dover et al., 1994; Collins et al., 1995; Maestri et al., 1996). The second is one of the phosphodiesterase V inhibitors prescribed in erectile dysfunction (Boolell et al., 1996a,b) and pulmonary hypertension (Prasad et al., 2000; Weimann et al., 2000; Ghofrani et al., 2004; Kukreja et al., 2004; Affuso et al., 2006). Two are the mechanisms underlying the cognition-enhancing effects of PBA in mouse models

of AD (reviewed in Cuadrado-Tejedor et al., 2011a, 2013). On the one hand, PBA is a chemical chaperone that may help in preventing the formation of protein aggregates. On the other hand, PBA is a histone deacetylase inhibitor that enhances the transcription of genes involved in memory processes. Inhibition of phosphodiesterase V is effective in AD models by increasing the concentration of cGMP that in turn enhances the neural mechanisms of defense against tau hyperphosphorylation and Aß aggregation (Rutten et al., 2007; Puzzo et al., 2009; Cuadrado-Tejedor et al., 2011b, 2013; Zhang et al., 2013; García-Barroso et al., 2013, 2014). Importantly, whereas acute treatment did not affect cognitive performance in healthy individuals (Reneerkens et al., 2013), a double-blind placebo-controlled study in patients with erectile dysfunction showed cognitive enhancement of a chronically administered phosphodiesterase inhibitor (Shim et al., 2014). Even in a chronic regime phosphodiesterase V inhibitors are safe (Montorsi et al., 2004; Giuliano et al., 2010; www.fda.gov/drugs/drugsafety/ucm390876.htm). To bridge the gap of successful "anti-AD" therapies in mice that do not reach humans (see Franco and Cedazo-Minguez, 2014), safe drugs could, in my opinion, be the first to test.

I consider that a non-for-profit organization such as the US FDA may take the lead to select 3–4 safe drugs, a couple of dietary supplements and a placebo, and design a longitudinal study that should start in late middle-aged healthy individuals with a lifelong follow-up. Such a study will take long to give results, but they would be quite robust and of better quality as time passes. In summary my opinion is that cognitive enhancers in the form of safe drugs and safe dietary supplements (vitamin C for instance[1]) should be tested already in individuals without clinical symptoms of dementia. Less informative but easier to implement would be to follow the age-dependent cognitive decay in patients taking already chronic medication for non-CNS indications that has shown (in mice) cognitive enhancing potential. Such studies would benefit of the most recent criteria of dementia/AD diagnosis, of novel behavioral tests and of novel biomarkers of preclinical phases of AD (Jack et al., 2011; Sperling et al., 2011). Likely, the results would indicate the potential of the assayed drugs for improving cognition and/or delaying onset of dementia, and the convenience or, otherwise, the inconvenience of starting medication in apparently healthy individuals. Even individuals not entering into dementia might benefit from reducing the cognitive decline due to aging.

[1]A recent report shows positive results of vitamin C in both wild type and the APP/PSEN1 animal model of AD (Kennard and Harrison, 2014).

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Rejuvenating procholinergic treatments for cognition enhancement in AD: current challenges and future prospects

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Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by global cognitive decline, with predominant impairments arising in attention and memory (Perry and Hodges, 1999). It is the sixth largest cause of death, and currently there is no way to prevent, cure, or even slow the progression (Klafki et al., 2006; Alzheimer's Association, 2014). Although there is a widespread decline in various neurotransmitter-containing cell bodies and axonal terminals in AD, the most consistent losses are seen in the basal forebrain (BF) cholinergic neurons and its projections (Mesulam, 2004; Schliebs and Arendt, 2011). Because of the documented role of the BF cholinergic system in learning and memory, the "cholinergic hypothesis" of AD was established (Bartus et al., 1982) and has been the primary directive for drug development and treatment in AD for almost three decades. While cholinomimetic drugs such as acetylcholinesterase (AChE) inhibitors, which elevate extracellular levels of the neurotransmitter acetylcholine (ACh), are the viable treatment option for AD and provide moderate alleviation to cognitive impairment, the magnitude of cognitive improvements with these drugs has remained limited (McGleenon et al., 1999; Raina et al., 2008). Additionally, these drugs are not successful in halting the progression of AD. Furthermore, the evidence that non-specific blockade of either muscarinic or nicotinic ACh receptors (mAChRs and nAChRs) alone produce dementia-like symptoms has remained inconsistent (Little et al., 1998; Erskine et al., 2004; Roegge and Levin, 2006). These issues have raised questions concerning the validity of the cholinergic hypothesis and whether the development of procholinergic therapies as cognition enhancers should be considered for AD. Here we argue that psychopharmacological approaches targeting the cholinergic system are based on previous conceptualizations of ACh regulating arousal states. We urge that emerging views from recent studies that refine our understanding of the cholinergic mediation of specific cognitive processes, and how cholinergic mechanisms interact with other pathological markers during the progression of AD, should be considered while designing procholinergic therapies. This discussion will also focus on the development of new drug candidates such as cholinergic receptor subtype-specific agonists, choline transporter (CHT) modulators and neurotrophin-based therapeutics to normalize cholinergic function in AD. Additionally, the need to combine multiple therapeutic approaches to slow AD progression and maximize cognitive benefits will be emphasized.

BF cholinergic neurons located in the medial septum, vertical and horizontal band of Broca, and nucleus basalis/substantia innominata complex innervate the cortical mantle, as well as the hippocampus. Traditionally, the BF cholinergic system was described as a diffusely organized neuromodulator system that influences information processing throughout the cortex and hippocampus in the awake brain and during REM sleep (Woolf, 1991). There are a plethora of neurophysiological studies that demonstrated that pairing BF stimulation with the stimulation of thalamic afferents enhanced the processing of sensory inputs, while the loss of cortical cholinergic inputs or administration of m/nAChR antagonists abolished this effect (Sarter et al., 2005). Additionally, a considerable amount of evidence generated from psychopharmacological and lesion studies indicated that the BF cholinergic system supports attentional functions, working memory, and memory consolidation (Furey et al., 2000; Power et al., 2003; Sarter et al., 2003). Furthermore, microdialysis studies illustrated performance-associated changes in ACh release in the cortex and hippocampus of rodents performing attention or memory tasks (Himmelheber et al., 2000; McIntyre et al., 2002). Together, these data suggested that the BF cholinergic system contributes to attention, learning, and mnemonic processes by generally inducing a state of arousal and elevating sensory processing by increasing the signal to noise ratio. Therefore, sustaining extracellular ACh release by terminating its highly efficient degradation process via AChE was considered a valid approach to restore cognitive function in AD.

AChE inhibitors have been in clinical practice to treat the cognitive symptomatology of mild to moderate AD for almost two decades. Tacrine was the first approved

AChE inhibitor for AD. However, due to a faster half-life and potential to produce adverse effects, specifically liver toxicity, it was replaced by newer AChE inhibitors such as donepezil, galantamine and rivastigmine (Knapp et al., 1994; Ma et al., 2003; Di Santo et al., 2013). Although AChE inhibitors have been shown to improve cognitive, specifically attentional, functions in AD subjects (Foldi et al., 2005), these improvements are ultimately inadequate and new procholinergic approaches are needed (Raina et al., 2008; Pepeu and Giovannini, 2009). One possible explanation for limited therapeutic efficacy of AChE inhibitors might be that besides stimulating the postsynaptic cholinergic receptors, higher levels of baseline ACh levels at the cholinergic synapses may also stimulate presynaptic autoreceptors, such as muscarinic M2 receptors, which may shut down the recruitment of cholinergic inputs during information processing (Decossas et al., 2005). Furthermore, the behavioral consequences of sustained postsynaptic m/n AChR activation remain unknown. The uncoupling of presynaptic from postsynaptic cholinergic signaling is hypothesized to have profound effects on the neuromodulation of local and efferent circuitry limiting cognitive enhancement (Hasselmo and Sarter, 2011).

Advancements in understanding the multi-temporal modes of cholinergic transmission offer insight into developing drug treatments centered on cognition enhancement. The recent evolution of a biosensor-based electrochemical approach for monitoring cholinergic transmission in real time generated evidence that precisely orchestrated and temporally restricted changes in ACh release mediated specific cognitive operations. In task-performing animals, phasic (rapid; on a sub-second to second time scale) increases in cholinergic transmission in the prefrontal cortex mediated the detection of attention-demanding cues by switching perceptual processing of the cue to cue-evoked activation of response rules (Parikh et al., 2007; Howe et al., 2013). Such transient increases in behavior-evoked ACh release were not observed in the motor cortex, which was used as a neocortical control region. Moreover, performance-related tonic (slower; on the time scale of minutes) increases in ACh release, which occurred cortex-wide, fostered and maintained general readiness for input processing, and facilitated signal-driven processes required for learning and maintaining attention. The pattern of tonic changes in cholinergic transmission resembled performance-related cortical ACh release measured using microdialysis (Parikh and Sarter, 2008). These temporally-dissociated characteristics of ACh release patterns are also supported by the electrophysiological evidence demonstrating burst firing and tonic discharges of BF cholinergic neurons (Unal et al., 2012). Collectively, these studies led to a major revision of our view on ACh that was previously considered as a slowly releasing modulator of arousal augmenting the gain function of neurons, to now, as a neurotransmitter that encodes distinct cognitive operations. This view emphasizes a need to focus on designing cholinergic therapies targeting the phasic component of cholinergic transmission that is critical for signal detection.

Harnessing this updated view of cholinergic transmission, specific ligands that activate α4β2 nAChRs may exert procognitive effects by amplifying cholinergic transients in AD subjects. Cortical cholinergic transients are generated based on local glutamatergic-cholinergic interactions (Sarter et al., 2009). Stimulus-driven recruitment of thalamocortical inputs increases glutamate release, which activates ionotropic glutamate receptors on cholinergic terminals and evokes phasic ACh release. These cholinergic transients foster detection of signals in attentional contexts, presumably by producing persistent spiking activity on cortical pyramidal neurons through postsynaptic mAChRs (Haj-Dahmane and Andrade, 1998). Activation of the high-affinity α4β2 nAChRs residing on thalamocortical afferents also produces phasic increases in cholinergic activity via similar glutamatergic mechanisms (Parikh et al., 2008, 2010). A similar conceptual framework is applied to septo-hippocampal cholinergic circuits for encoding of episodic memories (Hasselmo and Sarter, 2011). Thus, α4β2 nAChRs represent a valid biological target to develop procognitive drugs that act by facilitating phasic cholinergic signaling.

Another strategy would be to target cellular mechanisms that are involved in ACh production in cholinergic synapses and are critical to maintaining cholinergic transmission under conditions of higher cognitive load. The capacity to import choline into the presynaptic terminals via the high-affinity CHTs dictates the rate of ACh synthesis and release (Ferguson and Blakely, 2004; Sarter and Parikh, 2005). The mobilization of the intracellular pools of CHTs to the surface membrane (CHT trafficking) increases during attentional performance to maintain cholinergic transmission (Apparsundaram et al., 2005). Therefore, aberrations in CHT trafficking may influence phasic ACh release and attentional functions. In a recent study, we found that the capacity to generate cholinergic transients following sustained BF stimulation declined in CHT heterozygous mice (Parikh et al., 2013b). Moreover, these mutants displayed attentional impairments and disrupted trafficking of subcellular CHTs. These interesting results point toward an important role of CHT function in sustaining phasic cholinergic signaling to maintain cognitive functions. Given the evidence that high-affinity choline uptake declines in AD (Rodriguez-Puertas et al., 1994), future research on developing drugs that activate CHT function or increase the subcellular trafficking of CHTs holds promise to be a potential treatment for restoring cognitive deficits in AD.

An additional approach to developing procognitive therapies is targeting the interaction between BF cholinergic neurons, via n/m AChRs, and AD biomarkers. Among the neuropathological features of AD, the deposition of fibrillogenic β amyloid (Aβ) plaques and accumulation of intracellular neurofibrillary tangles containing hyperphosphorylated microtubule-associated protein tau are the two major hallmarks. Studies involving transgenic mice harboring mutations in AD-associated genes including amyloid precursor protein (APP), presenilin-1 and tau, have provided insights into possible reciprocal interactions between cholinergic markers and amyloidosis/tauopathy (Christensen et al., 2010; Perez et al., 2011). While it remains debated whether the cholinergic pathology is the primary cause or a consequence of AD, efforts to understand the relationship between cholinergic signaling and pathological

substrates of AD are critical to understanding the etiology of AD. The interactions between Aβ and α7 nAChRs have remained complex. For example, the loss of α7 nAChRs produced cognitive decline and accumulation of soluble oligomeric forms of Aβ in 5-month old transgenic mice harboring the mutation for APP gene (Hernandez et al., 2010). Conversely, the activation of α7 nAChR with Aβ was shown to produce tau phosphorylation (Hu et al., 2008), and the deletion of this receptor gene improved memory impairments, reduced gliosis and preserved long-term potentiation in aged mice modeling the key pathological features of AD (Dziewczapolski et al., 2009). These data present a scenario where α7 nAChR agonists represent a potential strategy for controlling cognitive deficits in early AD that mostly result from synaptotoxic effects of Aβ oligomers, while blocking α7 nAChR function could alleviate cognitive symptoms during advanced stages of AD mostly associated with Aβ plaque and neurofibrillary tangles.

There is some evidence that mAChRs regulate APP processing. Specifically, the loss of M1 mAChRs has been shown to activate amyloidogenic processing of APP and greater accumulation of amyloid plaques in APP transgenic mice (Davis et al., 2010). Since M1 mAChRs are predominantly expressed in the cortex and hippocampus and play a major role in attention and memory (Soma et al., 2014), targeting these receptors as a therapeutic candidate for AD holds promise in compensating for cholinergic hypofunction while controlling Aβ. Currently efforts to develop positive allosteric modulators for M1 mAChRs as potential treatment for AD are ongoing.

Besides the role of Aβ and tau, oxidative stress and inflammation have also been considered to account for neurotoxicity in AD. It is important to note that some of the modest cognitive benefits of AChE inhibitors (above) have been actually ascribed to their anti-inflammatory properties, which involve inhibition of cytokine production and antioxidant effects (Chao, 2003; Tabet, 2006). Although a direct link between central cholinergic mechanisms and inflammatory processes is still lacking, more research in this area may provide new avenues to design procholinergic therapies for mitigating inflammation in AD.

The most significant obstacle in bolstering cholinergic and cognitive function in AD is the progressive loss of cholinergic innervation and neurons (Schliebs and Arendt, 2011). This has spurred drug discovery efforts to focus on developing neuroprotective therapies to preserve cholinergic function in AD. Nerve growth factor (NGF) is the primary neurotrophic factor supporting the growth, maintenance, and survival of BF cholinergic neurons by binding to the high-affinity tropomyosin-related kinase A (trkA) receptor (Fagan et al., 1997). Moreover, activation of p75 NGF receptors is known to exert detrimental effects on neurons by triggering apoptotic pathways (Chao, 2003). Postmortem studies have supported the notion that the loss of trkA receptors, and presumably the imbalance between trkA and p75 signaling, contributes to cholinergic dysfunction in AD (Mufson et al., 2008). We previously demonstrated that selective reduction of trkA receptors on BF cholinergic neurons produces persistent attentional impairments and decline in phasic cholinergic signaling in aged but not young rats (Parikh et al., 2013a). Moreover cholinergic dysfunction in trkA-suppressed aged rats occurred due to age-related accumulation of proNGF and overactivation of proNGF-p75 signaling (Yegla and Parikh, 2014). We also found that Aβ oligomers produced robust impairments in presynaptic cholinergic signaling and attentional capacities in aged rats (Parikh et al., 2014). Because Aβ oligomers are known to interact with the extracellular domain of p75 and produce neuritic degeneration in neuronal culture prepared from BF cholinergic neurons (Knowles et al., 2009), oligomeric Aβ-induced dysfunction of cholinergic synapses may be linked to p75 activation. Collectively, these findings support the view that interactions between aging/pathological aging and neurotrophic signaling escalate the vulnerability of the BF cholinergic system and neurotrophin-based therapies may have potential to rescue the loss of this neurotransmitter system in AD. Therefore, neuroprotective strategies that provide trophic support to cholinergic neurons or that restore trkA/p75 balance may offer advantage over the current drugs to halt cognitive deterioration in AD.

Recent research confirms that the era of developing a "magic bullet" to foster cognition enhancement in AD is over. Therefore, we need to consider devising strategies that focus on a more integrated or holistic therapeutic approach to preserve cholinergic function and halt cognitive deterioration in AD. In an ideal scenario, a combination of drugs that augment phasic cholinergic signaling, block the interactions between the pathological markers of AD and the cholinergic proteome, and activate neurotrophic signaling will maximize cognitive benefits.

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An Integrated Approach for the Monitoring of Brain and Autonomic Response of Children with Autism Spectrum Disorders during Treatment by Wearable Technologies

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Autism Spectrum Disorders (ASD) are associated with physiological abnormalities, which are likely to contribute to the core symptoms of the condition. Wearable technologies can provide data in a semi-naturalistic setting, overcoming the limitations given by the constrained situations in which physiological signals are usually acquired. In this study an integrated system based on wearable technologies for the acquisition and analysis of neurophysiological and autonomic parameters during treatment is proposed and an application on five children with ASD is presented. Signals were acquired during a therapeutic session based on an imitation protocol in ASD children. Data were analyzed with the aim of extracting quantitative EEG (QEEG) features from EEG signals as well as heart rate and heart rate variability (HRV) from ECG. The system allowed evidencing changes in neurophysiological and autonomic response from the state of disengagement to the state of engagement of the children, evidencing a cognitive involvement in the children in the tasks proposed. The high grade of acceptability of the monitoring platform is promising for further development and implementation of the tool. In particular if the results of this feasibility study would be confirmed in a larger sample of subjects, the system proposed could be adopted in more naturalistic paradigms that allow real world stimuli to be incorporated into EEG/psychophysiological studies for the monitoring of the effect of the treatment and for the implementation of more individualized therapeutic programs.

Keywords: Autism Spectrum Disorders (ASD), quantitative EEG (QEEG), electrocardiogram (ECG), wearable sensors, monitoring, naturalistic, personalization, imitation

INTRODUCTION

Recent advances in neuroimaging and other less-invasive neurophysiological monitoring systems allow researchers to explore the relationship between neurophysiological signals, neurodevelopmental disorders and behavioral changes. In particular, atypical patterns of brain activity and connectivity have been documented in children with Autism Spectrum Disorders (ASD) and are the basis of impaired and atypical behaviors (Belmonte et al., 2004; Geschwind and Levitt, 2007; Coben et al., 2008; Cantor and Chabot, 2009).

Electroencephalography (EEG) is a non-invasive technique able to identify dysfunction in various brain regions in autistic individuals. EEG measurements can be investigated in the frequency domain, and it has been convincingly demonstrated that assessing specific frequencies can yield insights into the functional correlations between brain regions. The EEG patterns analysis in the frequency domain is known as Quantitative EEG (QEEG). Commonly QEEG has been used to capture electrical patterns at the scalp surface, which primarily reflect cortical electrical activity or "brainwaves" (Tong and Thakor, 2009). Recently, several studies have used QEEG as a tool for neurophysiological assessment of children with ASD during resting state condition or specific tasks (for a review see Billeci et al., 2013). Interestingly, QEEG measurements can provide a mean to establish treatment efficacy (Dawson et al., 2012). According to the above-mentioned evidence, QEEG provides sufficient sensitivity and specificity to be worthy of consideration for use in the diagnosis, treatment and outcome evaluation of neurodevelopmental disorders.

ASD are also characterized by altered autonomic function, which plays an important role in the regulation of behaviors during social interaction. Physiological parameters and vital signs including heart rate, systolic and diastolic pressure, pulse rate, skin conductance, body temperature, and fingertip temperature can be used as cues of autonomic functions. In particular, heart rate variability (HRV) is a well-recognized method to assess the cardiac autonomic balance of the autonomic nervous system (Goldberger, 1999; Friedman, 2007). Although a few parameters, such as the HRV, are influenced by physical activity, nevertheless they have been increasingly used to measure the activity of the autonomic nervous system and to study neurophysiological responses in naturalistic settings (Goodwin et al., 2006). Other studies have shown an extremely high autonomic arousal in individuals with ASD even though they appeared to be outwardly calm (Hirstein et al., 2001; Hoch et al., 2010; Ming et al., 2011).

One of the limitations of the physiological parameters' assessment protocol is the artificial setting in which signals are usually acquired, which may or may not be closely related with naturally occurring stimuli. Therefore, these protocols induce both systematic and non-systematic biases to the experimental outcome eluding the actual nature of the data. Furthermore, they do not allow an ecological assessment and monitoring during treatment or even at home.

The recording of physiological signals [such as electroecephalogram (EEG) or electrocardioram (ECG)] during treatment in a semi-naturalistic setting may reveal important cues about the engagement, the arousal and emotional state and can support clinicians during therapeutic sessions in the implementation of the most appropriate personalized treatment plan.

The study of engagement is particularly relevant in ASD as deficits in this field (that is when the child is not able to share his/her attention to the other) emerge very early, in the second half of the first year of life, leading to reduced engagement with social stimuli, and subsequently reduced opportunities for social learning (Dawson et al., 1998; Mundy and Neal, 2000; Chevallier et al., 2012). These early deficits may thus have cascading effects on social communication development in successive years. In order to contrast these cascading effects evidence-based models (i.e., Early Start Denver Model) suggest building therapeutic tasks around specific engagement skills (i.e., imitation or joint attention) as core of the intervention (Billeci et al., 2016; Bono et al., 2016). During these tasks in which there is a social interaction with a therapist, it is possible to explore the response to social engagement and emotion regulation in response to social disengagement (that is when the child is not involved in social attention). In particular in the last years some studies have been performed, which provide evidences that physiological signals could constitute an important marker of social functioning and well-being that differentiate between engagement and disengagement during social interactions or treatment sessions (Patriquin et al., 2013; Di Palma et al., 2016; Shahrestani et al., 2016).

It is important to underline that monitoring physiological parameters during therapeutic sessions or during daily basis routines is definitely more challenging than monitoring the same parameters under controlled conditions. It is mandatory for example that the equipment should not interfere with the activities performed by the children during the treatment session. Wearable systems and wireless technologies can overcome this problem allowing monitoring subjects in an unobtrusive way (Varshney, 2005, 2006; Yilmaz et al., 2010).

The present study aims at describing and discussing the implementation of a wearable technology system that can be used during naturalistic interactions between a child and a clinician during a treatment session for the monitoring of brain and autonomic response. A preliminary application in a sample of children with ASD is presented. This work has been carried out within the framework of MICHELANGELO, a project funded by the European Commission (FP7- ICT-288241) (http://www.michelangelo-project.eu/).

The combined analysis of QEEG and ECG signals in semi-naturalistic settings enables simultaneous examination of neurophysiological and physiological correlates while the child is engaged in socio-emotive interactions. This system is able to provide (i) ecologically synchronized quantitative measurements of brain signals, and (ii) autonomic responses not measurable with traditional research methods within a natural environment. For this purpose, wearable technologies for EEG and ECG have been used, which are suitable for young children with ASD. The system proposed will allow a reliable indication of brain activity and autonomic status in a naturalistic setting contributing toward the implementation of more individualized and effective treatment for children with ASD.

MATERIALS AND METHODS

Participants and Paradigm

The system was tested with five children with ASD (all males, age range = 6–8 years, mean age = 7.2 ± 0.83 years) (**Table 1**). The study was approved by the IRCSS Stella Maris Foundation's Ethical Committee and all the parents signed a written consent form to participate.

The ASD diagnosis was formulated according to the DSM-5 criteria (APA, 2013) and confirmed by the Autism Diagnostic Observation Schedule-2 (ADOS-2, Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R, Lord et al., 1994).

The ADOS-2 diagnostic algorithm also provides an algorithm for computing the comparison score (CS), a measure of the severity of autism-related symptoms. The CS ranges from 1 to 10, where 1 indicates minimal-to-no evidence of autism-related symptoms and 10 indicates a high level of impairment.

The adaptive behavior was assessed according to the Vineland Adaptive Behavior Scale-II (VABS-II, Sparrow et al., 2005). A multidisciplinary team—including a senior child psychiatrist, and two clinical child psychologists experienced in ASD—conducted the diagnostic assessment during a 5-day extensive evaluation. The Wechsler Intelligence Scales for Children-IV (WISC-IV) were used to assess the Full Scale Intelligence Quotient (FSIQ).

The children involved in the experiment were monitored during one therapy session in clinic with the integrated system. The semi-naturalistic experimental paradigm was based on imitation (IM) in the context of a play-based setting (**Figure 1**). Each session took about 15 min. During all the session the children remained seated on a chair playing at a table with the therapist in order to limit artifacts in the data acquired.

The IM phase is realized according to three different tasks in which the therapist asks to the child to imitate what she is doing. In task 1, the therapist uses blocks, play-doh, or sheets and markets in order to elicit functional imitation in the child; in task 2 the therapist suggests the child gestural and symbolic imitation; in task 3 the therapist elicits facial expressions in the child. Each task was repeated sever times in order to have several segments of the signals, which could be mediated to have more consistent results. During the experimental sessions data brain, autonomic and video data were recorded and analyzed in post-processing with the integrated platform described in the following paragraphs.

Design

General Overview

The overall architecture of the integrated system is shown in **Figure 2**. It mainly consists of three modules: the biosignal sensor unit, the video mobile unit, and a Central Unit (CU).

The main function of the biosignal sensor unit is the wearable and wireless acquisition of EEG and ECG signals while allowing the child to interact with the therapist. The unit is composed by the Enobio wireless device (STARLAB, Barcelona, Spain) for EEG recording (Cester et al., 2008) and by a wireless ECG chest belt (Solar et al., 2012).

The integrated system is also provided of data analysis toolboxes for the processing of the recorded video, EEG and ECG signals. The collected data can be loaded and queried for data visualization, segmentation, and feature extraction. The toolboxes are developed as a research tool in order to investigate physiological and behavioral parameters correlated with behaviors of the child during treatment sessions. The main components of the system are described in the following paragraphs (for details about EEG and ECG feature extraction see Supplementary Materials).

Biosignal Sensor Unit

Enobio offers a high degree of unobtrusiveness (easy to use, wearable, only 65 grams weight). Each active digital electrode with a transduction interface and electrode is able to acquire, digitize, and transmit the signal on site in order to reduce the environmental noise while recording data away from the lab or controlled environments.

The system continuously records EEG signals over 19 channels positioned according to the 10/10 standard scheme and two references (placed on the mastoid), at 500 Hz with a 16-bit accuracy. Enobio is equipped both with gel and dry electrodes. While gel electrodes provide a better contact with the skin and lower impedance, their positioning can be very long and uncomfortable for the child. In this setting dry electrodes are chosen as they offer a shorter and easier set-up time comparable with gel electrodes, which is particularly important with children with ASD. Several articles indeed show that dry electrodes can yield performance comparable to gel electrodes (Zander et al., 2011; Guger et al., 2012). Data from Enobio are recorded by a dedicated software (NIC, Neuroelectrics).

The chest belt for ECG acquisition is a wearable device designed by our group based on the Shimmer® (Burns et al., 2010) wireless base module, which is CE certified and validated prior to the present study in a group of healthy subjects (Solar et al., 2012).

The system is powered by a 3.6 V rechargeable battery, which allows up to 7 h of continuous monitoring per charge. The system sample frequency can be set from a minimum of 100 Hz up to a maximum of 500 Hz. The hardware module was tailored to be compliant with the common cardio-fitness Polar™ or Adidas™ chest straps in order to gain in ergonomics, to be lightweight and allow long-term monitoring. These straps are fully washable and integrate dry electrodes applied directly to the patient's skin for single-lead acquisitions.

Video Mobile Unit

The video mobile unit is made up by two environmental cameras with a frame rate of 25 fps and a resolution of 640 × 480 for video recording. The cameras are wired and synchronized with the system to contextualize the neurophysiological parameters with the behavior of the child. With the aim of building an exploitable research tool to investigate EEG signal, inexpensive webcam were used as video capture devices (Microsoft LifeCam HD-5000).

TABLE 1 | Participants characteristics.

Subjects	Age in years	Diagnosis	ADOS-2 Module	ADOS (CS)	WISC-IV-FSIQ	VABS-II Composite
Child 1	7	Autism Spectrum	2	6	117	75
Child 2	8	Autism Spectrum	3	6	98	76
Child 3	6	Autism Spectrum	3	7	97	85
Child 4	7	Autism Spectrum	3	5	84	76
Child 5	6	Autism Spectrum	3	6	123	85

CS, Comparison Score; WISC-FSIQ, Wechsler Intelligence Scale for Children—Full Scale Intelligence Quotient; VABS, Vineland Adaptive Behavior Scale.

Central Unit

The CU (OS: Win8, RAM: 4 GB, CPU: Intel Core i5-3450—3.1 GHz—4 core) is positioned in the monitoring room and enables researchers to monitor the child during therapy and the neurophysiological signals. The monitoring room is located next to the therapy's room allowing the Bluetooth data transmission from the biosignal sensor unit and the video mobile data recording. Raw data are real-time displayed within *four* windows (ECG, EEG, Videos) as shown in **Figure 3**.

The CU manages the connection between the monitoring interface and the set of biosignal sensors and video mobile units, in particular the CU is responsible for notifying the "Start Session" message to all the recording units (RUs) involved and initializing each new session. All the communication between the CU and the RUs is transmitted in a validated XML format v1.0. The application manages security and privacy, real-time streaming and data synchronization. In particular the synchronization among the different devices is guaranteed by the fact their applications run in the same system and are launched simultaneously by an application running on the CU.

After data collection, the data analysis toolboxes running in the CU are able to analyze and process the collected data off-line by combining different data as a whole data source.

Video Analysis Toolbox

The video analysis toolbox allows the labeling of the children's behaviors in the recorded session and is based on the Dante annotation tool (Cruciani et al., 2011) customized for the labeling of behaviors of children with ASD.

Some of the behavioral features extracted are considered as instantaneous features (i.e., gesture), while others represent a state of the subject that persists in time (i.e., engagement).

The video analysis tool provides a Graphical User Interface (GUI) (**Figure 4**) to re-play the video of a recorded session, while examining annotated data and the integration of EEG/ECG data.

A manual annotation grid, referring to the child and the therapist, allows behavioral analysis of the therapeutic session, as defined in the coding scheme.

The grid distinguishes between "States" and "Behaviors." States identify behavioral states of a subject that persist for a given duration in time, for example Engagement and Dis-Engagement. States are always considered as mutually exclusive. In contrast, Behaviors are always considered as instantaneous events, meaning that the corresponding event will have the same timestamp for Start Time and End Time.

The Video Analysis interface produces an "Event File," an. xls file containing the information about the annotated events (type of state/behavior, Start Time, End Time). Through the annotation of these events, each therapy session can be analyzed to provide contextual information on significant behaviors of the child, useful for exploratory analysis of EEG/ECG signal.

EEG Analysis Toolbox

EEG signals are first-pre-processed using EEGLAB Toolbox (Delorme and Makeig, 2004) to remove noise and artifacts. The recorded EEG signals are high passed at 0.5 Hz to get rid of noise from breathing and low passed at a cut-off frequency of 70 Hz to get rid of the high frequency noise. A Notch filter (45–55 Hz) is also applied to remove power line interference.

Ocular and muscular artifacts are first removed by visual inspection. In particular blink artifacts are identified as segments of data having deflection >150 μV, while ocular flutters, or muscle movement artifacts as segments having deflections of 50 μV relative to baseline. Segments containing these artifacts are excluded from the following analyses. In addition bad channels are removed using the "channel statistics" tool of EEGLAB. On the basis of these statistics "bad" channels were considered as the ones that had distributions of potential values that were further away from a Gaussian distribution than other scalp channels, and they were remove from further analysis.

After artifacts removal baseline signal is removed form data acquired during the task.

After-pre-processing, EEG data are imported in a home-made Matlab analysis toolbox for QEEG analysis.

First, the Power Spectral Density (PSD) is evaluated by transforming the signal from the time domain to the frequency domain using the Welch method (Welch, 1967). Then the absolute and the relative power of each band (delta: 1–4 Hz, theta: 4–7 Hz, alpha: 8–13 Hz, beta: 14–29 Hz, and gamma: 30–70 Hz) are computed for each electrode. Relative powers are usually more reliable than absolute powers because they show less variability among different subjects and they are less affected by artifacts (Duffy, 1986). Inter-hemispheric asymmetry is computed by the Brain Symmetry Index (BSI) (van Putten et al., 2004). The BSI is calculated within each EEG band considering the total power in each region (frontal, temporal, central, parietal, and occipital) of the left and right hemisphere (sum of the electrodes).

The connectivity between brain regions is estimated with the calculation of coherence, which gives an estimation of the

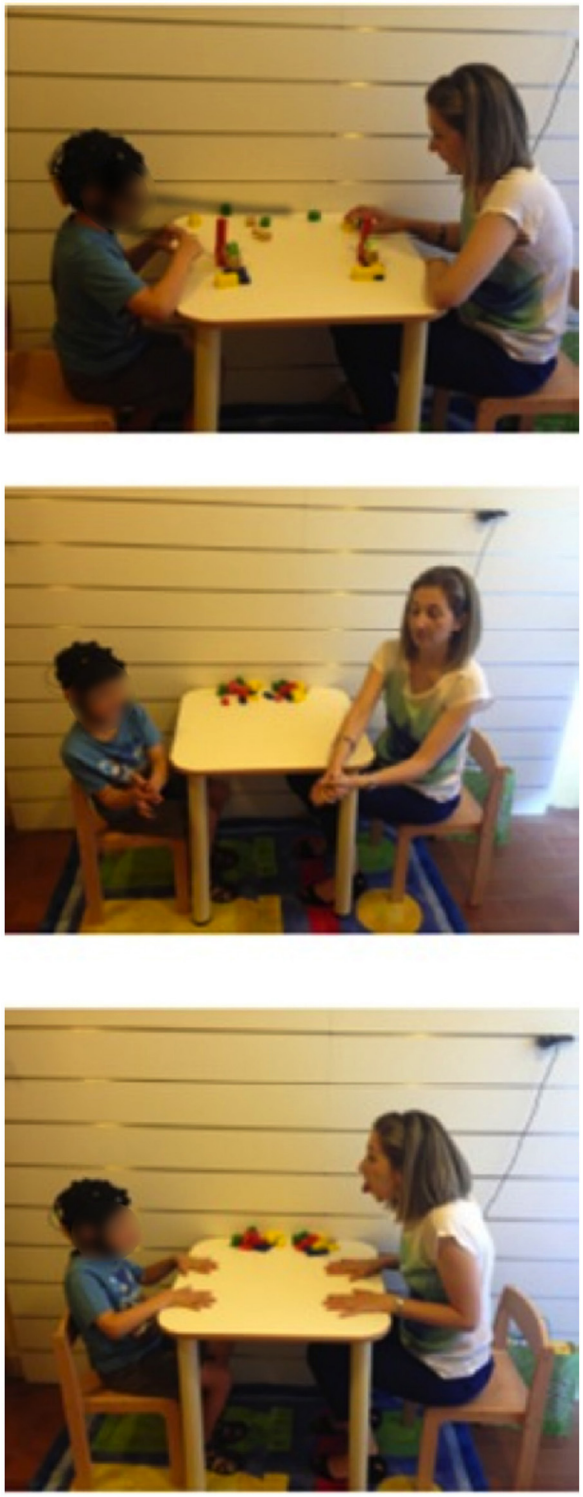

FIGURE 1 | Experimental paradigm.

linear correlation between two signals collected at two different scalp points as a function of frequency (Otnes and Enochson, 1972). Coherence is calculated for each pair of electrodes in each frequency band.

ECG Analysis Toolbox

ECG signals are pre-processed through a stepwise filtering process aimed at removing typical ECG artifacts and interferences. In particular, the baseline wander due to body movements and respiration artifacts are removed using a cubic spline 3rd order interpolation between the fiducial isoelectric points of the ECG (Jane et al., 1992). The power line interference and muscular noise are removed using an IIR (infinite impulse response) notch filter at 50 Hz and an IIR low pass filter at 40 Hz. In the final step of the pre-processing phase the Pan-Tompkins method is applied to detect the QRS complexes (Pan and Tompkins, 1985). The tachogram and the HRV are extracted according to the International Guidelines of HRV (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). The tachogram is a vector whose elements represent the beat-to-beat interval between *two* adjacent R peaks in the ECG allowing the definition of useful features for a further quantitative analysis. At this step the tachogram signal might not be suitable yet for a proper features extraction due to the presence of possible residual movement artifacts and outliers, which can be easily detected by visual inspection. Artifact are visually identified and removed. In order to prevent the signal from excessive shortening, the user should operate a careful artifacts selection choosing the interval to remove as tight as possible. Outliers are replaced by division or summation. Division is applied when the outlier is determined by a failure to detect an R-peak while summation while it is caused by faulty detections of *two* or more peaks within a period representing the R-R interval.

After pre-processing significant features, which could give an indication of the engagement of the child during the therapy are extracted from the ECG signal. In particular the Heart Rate (HR), the Root Mean Square of the Successive Differences (RMSSD), and the Respiratory Sinus Arrhythmia (RSA) are selected. The HR measures the number of poundings of the heart occurring in a specific lapse of time and it is typically expressed as beats per minute (bpm). The RMSSD, indicator of vagal activity, was chosen as a time domain measure of the HRV. The RSA refers to the periodic fluctuations in HR that are linked to breathing. RSA is largely determined by vagal influences on the heart, providing a noninvasive index of parasympathetic activity, social functioning, and cognitive performances (Patriquin et al., 2013, 2014). The RSA component from tachogram signal is extracted using the Empirical Model Decomposition (EMD) (Balocchi et al., 2004).

Data Collection and Measurement Definition

Data were collected using the technological platform described above during a therapeutic session of each participant included in this study. The Biosignal Sensor Unit and the Video Mobile Unit were connected to the CU and a new acquisition session was recorded for each child. The EEG data were acquired using Enobio at 500 Hz while for ECG signals a sampling frequency of 200 Hz was chosen to avoid too much noise and to optimize data transfer.

Data collected were analyzed in post-processing. Each recording session was first imported in the "Video analysis toolbox" and then coded by clinicians who reviewed the videos to define the events of interest. In particular, in this study we focused on the alternation of the "States," i.e., the Engagement and the Disengagement, during the therapeutic session.

Two coders were trained to use the coding system, by observing and coding videos of children with ASD, who were not included in the study. The 1 month training period enabled the coders to become familiar with the meaning of the features, to identify them correctly, and to acquire ability in coding procedures. The coders were required to achieve a satisfactory level of agreement between them (Cohen's Kappa $\geq$0.70) and with two expert clinicians (AN and SC) for each Event behavior (imitation) and for each State behaviors (Engagement and Disengagement).

The tolerance window regarding time discrepancy between coding was set at 1 s for event behaviors and at 3 s for state behaviors. The coding recorded outside these windows was reported as a coding error and was considered a disagreement. Intercoder agreement was calculated for each item, and the values of k were $\geq$0.70.

The mean Intercoder reliability showed satisfactory agreement ($k = 0.81$). In order to verify the ongoing agreement, 25% of the collection of sequences were coded by both coders.

The mean Intercoder agreement calculated on these sequences was $k = 0.84$, and the values of k were ≥ 0.70. In all cases of discordance between coders, the expert coders advice was used.

For a definition of a baseline, both for EEG and ECG, signals were acquired for about 3 min before the beginning of the task.

The Event File containing the information about coding was used to extract EEG and ECG segments in order to link different physiological patterns with different states of the children.

For the EEG analysis, data acquired were divided in "Engagement" and "Disengagement" states using the information contained in the Event File. First the segments were imported in the EEGLAB Toolbox and pre-processed. The baseline signal was removed from the two state signals. The cleaned segments were then imported in the QEEG analysis GUI to extract features of interest. The proportion of data retained after cleaning was not different between Engagement and Disengagement phases (Engagement: 7.34%, Disengagement: 7.85%). Finally, features extracted for each segment type of each type of State were averaged.

For the purpose of data reduction, *four* EEG lead-groupings were considered to compute coherence (Coben et al., 2008; Machado et al., 2015; see Supplementary Materials).

ECG data were imported in the ECG analysis GUI and after pre-processing relevant features were extracted. The tool generates plots, which show the trend of the features over time, and also stores data for a further numerical analysis. To evaluate how the therapeutic stimuli influence the cardiac activity, physiological events were defined for each feature when the parameter undergoes or exceeds established values. A crucial step lies in the definition of thresholds, which denote the occurrence of a physiological event related to the feature of interest. Reference values were customized for each child at each acquisition since environmental, subjective, and current emotional states could heavily affect the HR baseline.

The values for "higher HR" and "lower HR" were respectively calculated by the 90th and the 5th percentile of the baseline signal. The event of "lower RMSSD" referred to values undergoing the 20 ms threshold and denoted more effective participation from the child (Althaus et al., 1999). The threshold for "lower RSA" ranged in an interval from 6.3 to 6.5 ln(ms^2) (Porges et al., 2013).

For each State the mean and the standard deviation of the feature extracted as well as the percentage of physiological events detected were recorded. The percentage of physiological events was evaluated as the ratio of occurrences of the events to the total engagement time The approach described allowed to evaluate, both with a visual and a quantitative method, the physiological response of the child to the stimuli received with distinct reference to the different phases identified during the treatment.

Data Analysis

A preliminary statistical analysis was performed to evaluate differences in the features extracted between Engagement and Disengagement. Statistical analyses were performed in SPSS (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was applied to test the normality of the variables. For normal distributed variables a paired-samples t-test was applied, while for nonparametric variables a Wilcoxon-test was adopted. Results were considered significant for $p < 0.05$.

RESULTS

Feasibility Evaluation

The children did not show sensory-motor and/or behavioral issues in wearing the devices and completing all the tasks, administered within a friendly, and supportive environment without any difficulties or constraints.

We used labeled data generated through Manual Annotation to validate the system. In particular, the synchronization between Video and the other signals was crucial, since the video was the reference for the validation process. However, the required constraints on synchronization were not particularly strict considering that:

- the Video footage, which is the reference, has a frame rate considerably smaller compared to the EEG sample rate (25 vs. 500 Hz);
- even in behavioral annotation performed by a trained psychologist, a lag of 1 s is acceptable.

Therefore, the residual synchronization error due to the latency time between the data sampling and the reception by the synchronized machine is marginal considering that, whatever is the instant annotated as the start of the State, we considered the whole duration of the State for the analysis.

The synchronization tests have been performed by inserting a spike in the signal and comparing the video timestamp with the sensor data timestamps. The resultant accuracy with this setup is in the order of tenths of second, which is acceptable for our purpose.

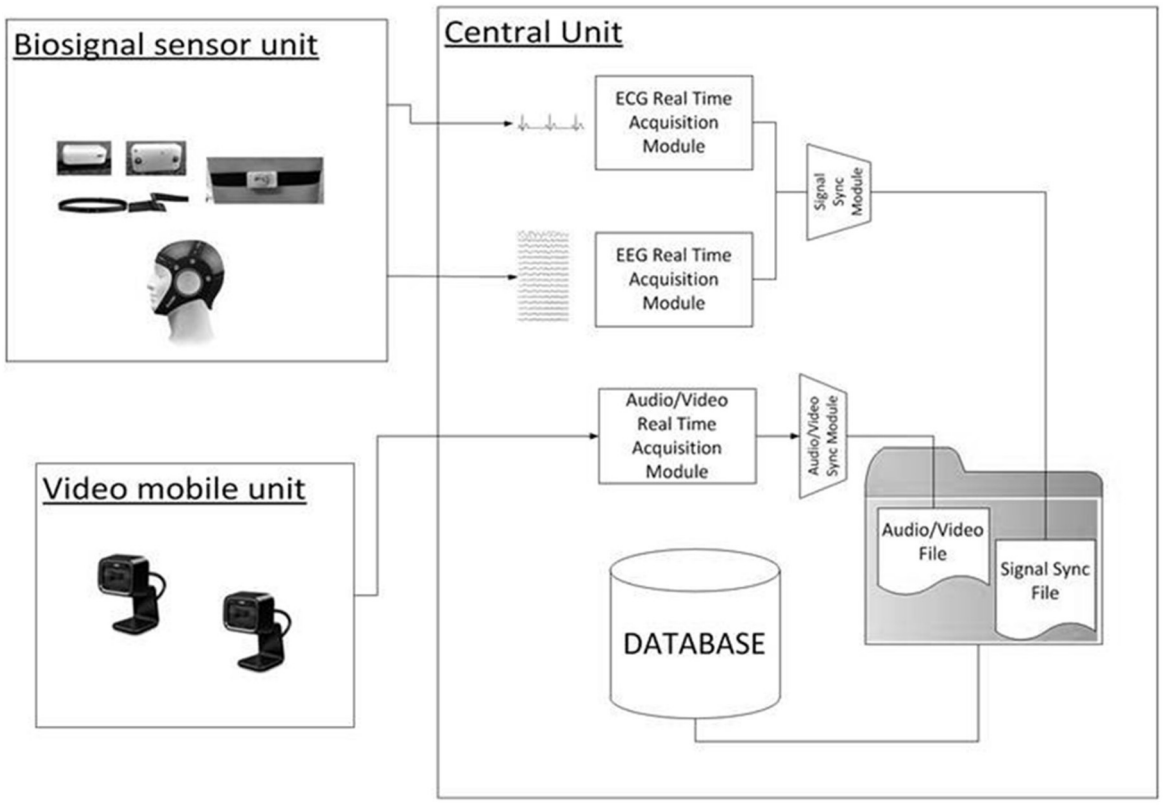

FIGURE 2 | Architecture overview.

EEG Results

Although each child showed his own individual pattern of brain activity and connectivity, all the children displayed visible changes of EEG pattern between the Engagement and Disengagement phases. Some of these changes were common among all the children and are summarized hereafter.

Figure 5 shows the location of the electrodes with statistically significant differences in PSD between Engagement and Disengagement phases.

Almost all the children displayed a significant relative power increase in most of the brain regions during the Engagement (**Figure 5**). At a group level analysis all the children showed significant power increase in frontal regions in delta band ($p = 0.04$). All but one child (Subject 3) also exhibited power increase in parietal regions in beta band ($p = 0.04$) and in occipital areas in theta, alpha, beta and gamma bands ($p = 0.04$). In Subject 3 there was not a significantly change in the PSD between Engagement and Disengagement in these frequency bands.

In the Engagement a transition from leftward to rightward asymmetry could be observed for almost all the frequency bands over the parietal areas. In particular this shift was significant in alpha and beta bands ($p = 0.04$). There was also a significant transition from rightward to leftward asymmetry in temporal areas in gamma band ($p = 0.04$).

Figure 6 shows statistically significant difference in coherence (coherence Engagement–coherence Disengagement) at the different cortical regions, in the different frequency bands.

A widespread increase of coherence was observed in almost all subjects during the Engagement in particular in theta, alpha and beta bands (**Figure 6**). The group level analysis revealed a significant increased in intrahemispheric coherence in posterior right and left areas in theta, alpha and beta bands ($p = 0.04$). Interhemispheric coherence increased at a central level in alpha and beta bands ($p = 0.04$) and at posterior level in beta band ($p = 0.04$). Although not significant at a group level analysis, it is possible to observe an increase of coherence in anterior regions in alpha band in almost all the subjects.

ECG Results

The system proved that the cardiac activity is strongly influenced by social engagement states and the ECG patterns turned out to be subjected to similar changes in the five subjects in response to changed psychological conditions. **Figure 7** shows example of plots of the HR, RMSSD, and RSA trends over time during acquisition intervals for Subjects 1 and 3, corresponding to the Engagement and Disengagement phases. Markers locate physiological events according to the thresholds previously described. The ECG analysis showed a clear correlation between

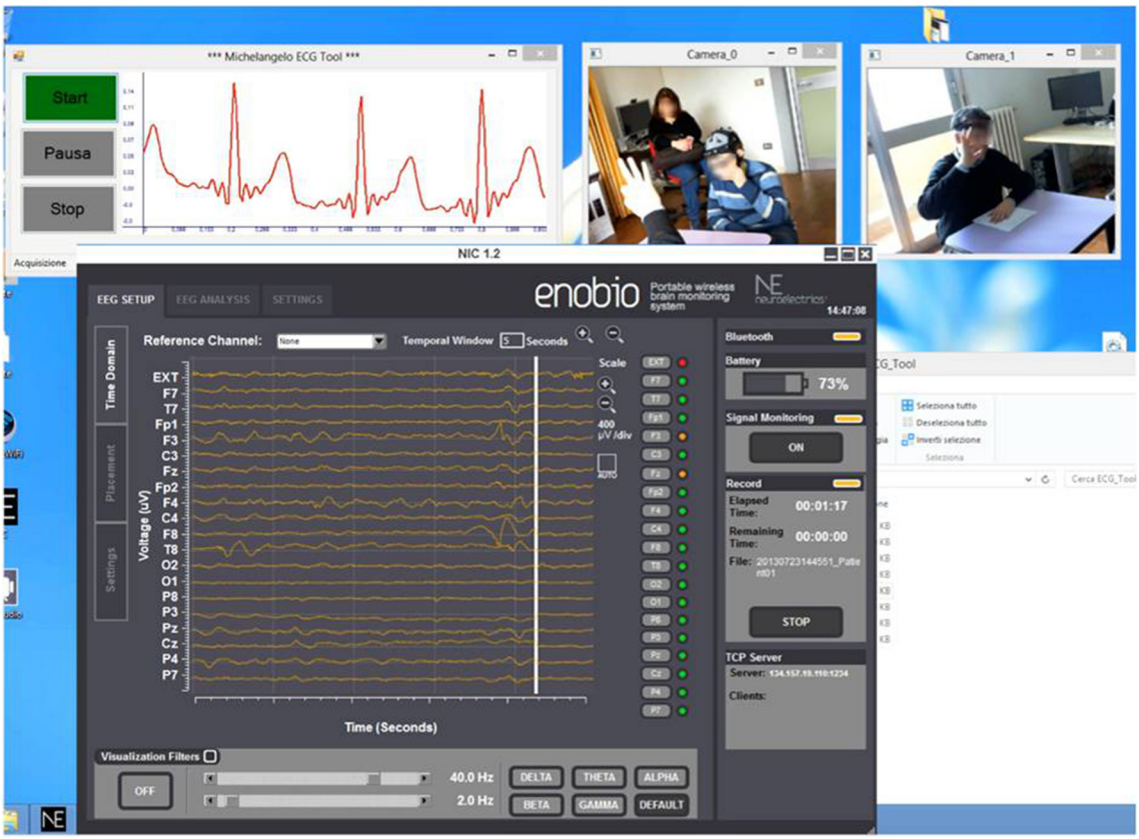

FIGURE 3 | Real-time acquisition of two camera video, ECG signal, and EEG signal during a therapeutic session.

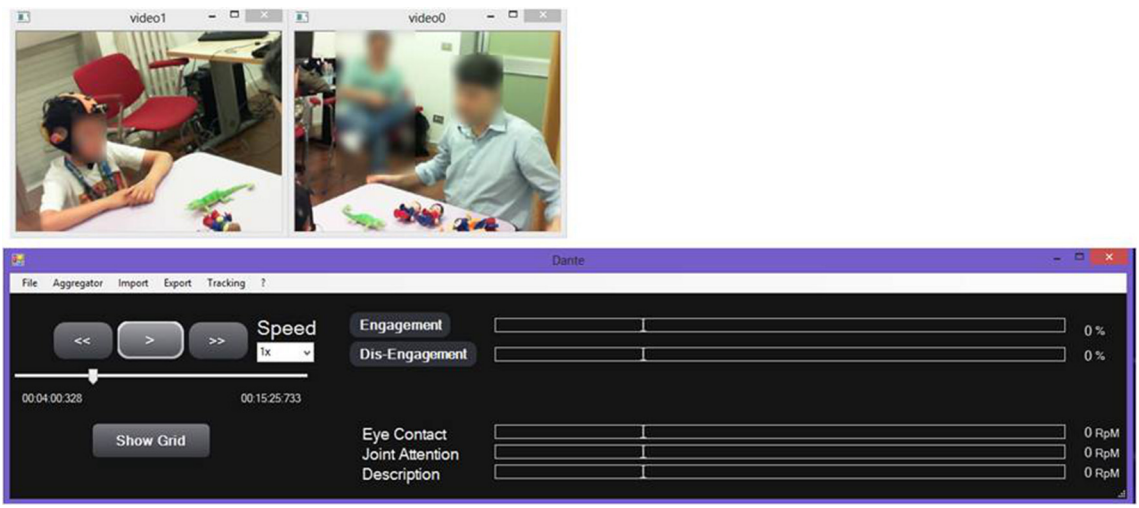

FIGURE 4 | Graphical User Interface for re-play and annotation of the recorded video session.

the detection of physiological events and the child's degree of involvement in the therapy. The plots reveal a greater presence of physiological events of "higher HR" and "lower HRV" and "lower RSA" in the Engagement as compared with the Disengagement. It was also evident that subjects displayed a remarkable RSA suppression compared with basal values in the Engagement. Furthermore, "lower HR" values turned out to be more frequent during the Disengagement.

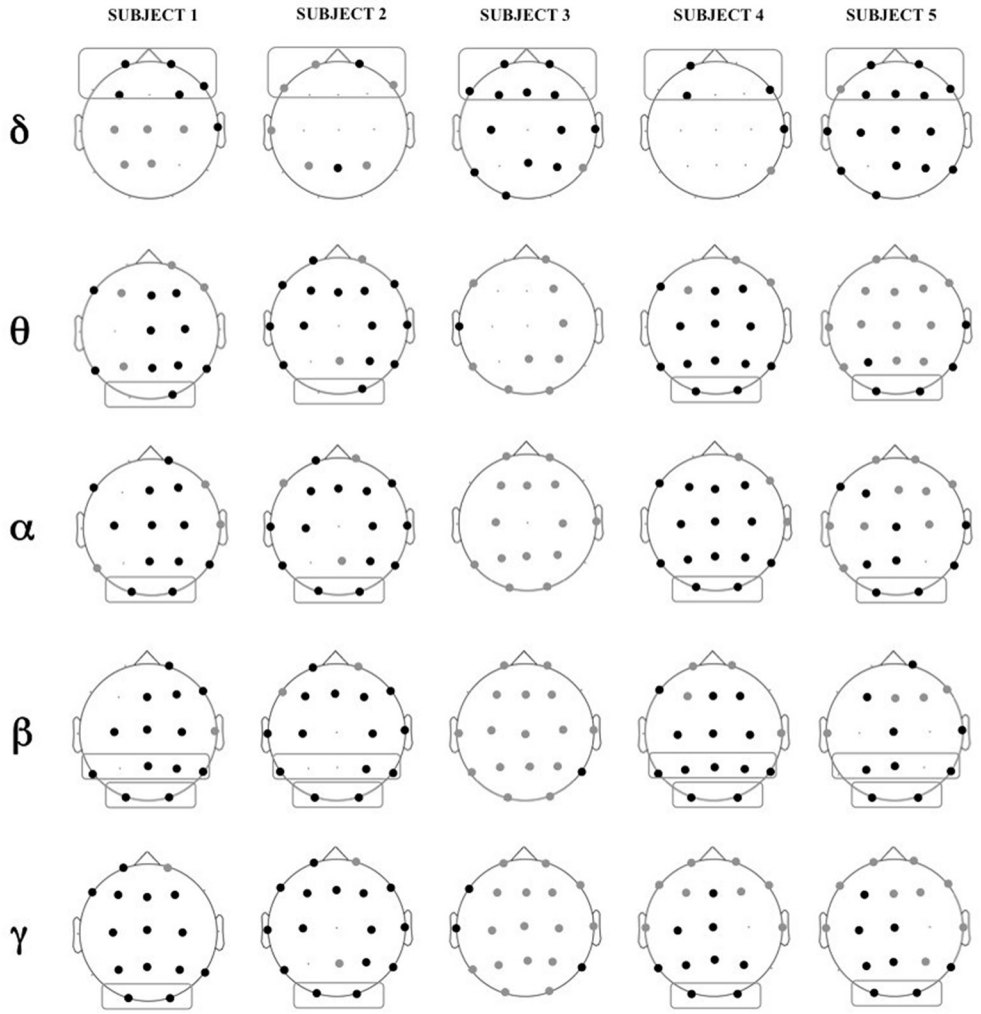

FIGURE 5 | Location of electrodes with significant differences in relative power in Engagement vs. Disengagement phase for each subject in each frequency band: black dots represent location of increase, gray dots location of decrease. Boxes represent brain regions with significant increase in relative power at a group level analysis.

Table 2 shows that children displayed an increased mean HR and a slightly significant greater percent number of "higher HR" physiological events during the Engagement compared to the Disengagement, excluding Subject 5 ($p = 0.07$). The mean RMSSD and mean RSA generally decreased during Engagement: therefore, the percent number of "lower HRV" and "lower RSA" events was significantly increased ($p = 0.04$ and $p = 0.005$ respectively).

DISCUSSION

The aim of this study was to develop and test innovative technologies to overcome some limitations of the present applications of physiological assessment in ASD (Bölte et al., 2016), including the artificial and constrained situations in which data are acquired and the need of a special compliance from the subjects, which prevented an ecological assessment so far.

This preliminary work represents an initial step to study the social cognition from an interactor point of view, based on the assumption that there is something fundamentally different when we are actively engaged with others in real-time social interaction as compared to when we merely observe them (Pfeiffer et al., 2012). The main contribution of this approach is that, if validated in a larger sample of subjects, would allow for more naturalistic paradigms that allow real world stimuli to be incorporated into EEG/psychophysiological studies.

In this pilot study, we have presented a paradigm for the acquisition of neurophysiological and physiological signals in a semi-naturalistic setting where children can interact with the examiner and play with different objects. Particular efforts have been provided to customize the ECG hardware, to integrate the videos, the ECG and the EEG units and to realize a user-friendly toolbox for data analysis.

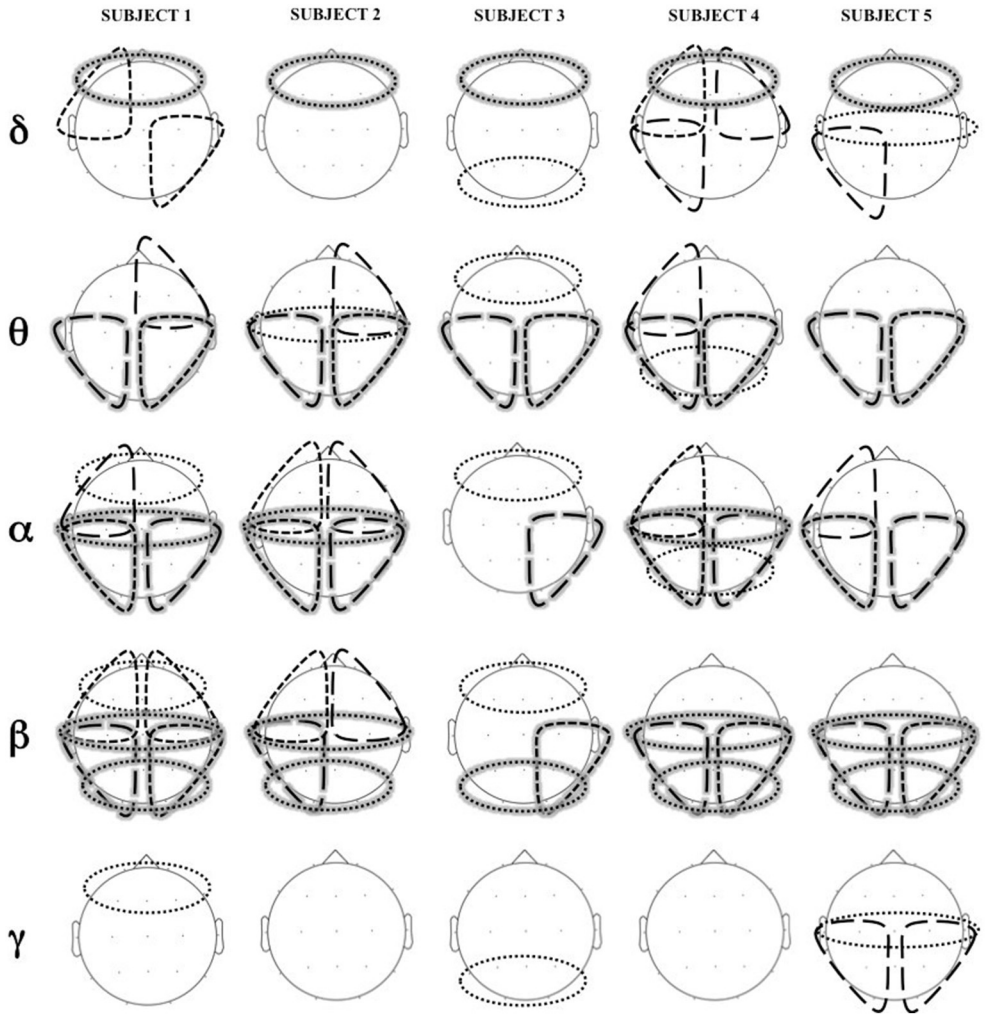

FIGURE 6 | Areas of significant increase in coherence in Engagement vs. Disengagement phase for each subject in each frequency band. Long dashed lines represent transversal coherence while short dashed lines represent short coherence. Shaded areas represent regions of significant increase at a group level analysis.

The wireless EEG cap and the chest strap containing the ECG demonstrated how unobtrusive tools can be suitable for young children and can be used with semi-naturalistic paradigms. This study confirmed our previous results about the feasibility of the application of wearable sensors and wireless technologies in young subjects with neuropsychiatric disorders (Billeci et al., 2015). The interaction with the examiner rather than with a screen like in most EEG paradigms, is another very important feature of this study, and allows recreating a more real situation with social interactions and cues. In this paradigm, we can assume that the signals acquired from the brain and the autonomic system are much more similar to what is generated while the child interacts in common life situations. This setting, relatively simple to be implemented, can be considered as one step toward a more behaviorally-driven analysis of neurophysiological activity.

The acquisition of physiological signals during treatment could provide important cues about the response of the child, which is commonly just observed from a behavioral point of view by clinicians. This can be extremely important to objectivize the effect of the treatment and to implement more effective therapies.

In particular, literature shows the importance of the QEEG technique for assessing brain connectivity and for the development of an individualized treatment program (Billeci et al., 2013). Previous QEEG studies showed how autistic children have differences in power spectra, coherence, and symmetry measures with respect to controls (Cantor and Chabot, 2009). This is true both when signals are acquired in a resting condition, with open or closed eyes, and when specific tasks are performed (Cantor and Chabot, 2009). Furthermore, it has been observed that it is possible to link a specific pattern of brain activation, characterized by specific features, to certain specific behaviors.

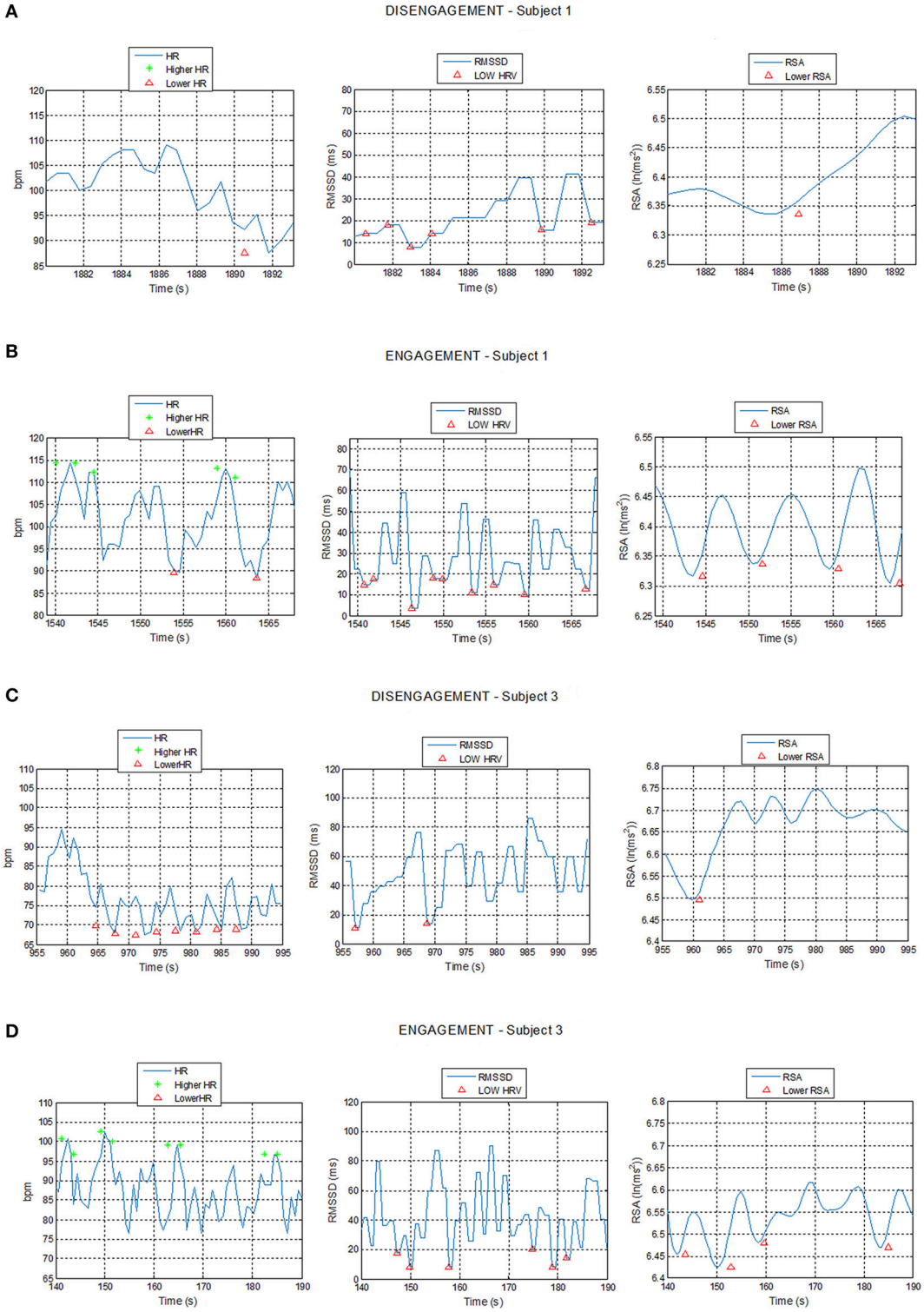

FIGURE 7 | Plot of Heart Rate (HR), Root Mean Square of the Successive Differences (RMSSD), and Respiratory Sinus Arrhythmia (RSA) trends during Disengagement (A,C) and Engagement (B,D) for Subject 1 and 3 with detection of physiological events: star markers represent HR value exceeding the high HR threshold while triangular markers represent HR, RMSSD, or RSA values undergoing the low HR, low RMSSD, and low RSA thresholds respectively.

TABLE 2 | Mean, Standard Deviation (SD), and percent number of physiological events for HR (bps), RMSSD (ms), and RSA (ln(ms^2)) values during Engagement and Disengagement.

Subjects	Feature	Disengagement		Engagement	
		Mean ± SD	%Physiological events	Mean ± SD	%Physiological events
Subject 1	HR	104.33 ± 3.21	15.8	104.68 ± 3.11	16.80
	RMSSD	36.22 ± 5.65	45.16	28.78 ± 5.53	47.64
	RSA	6.36 ± 0.05	3.22	6.36 ± 0.03	6.65
Subject 2	HR	97.64 ± 9.61	9.09	100.03 ± 9.29	16.63
	RMSSD	38.94 ± 14.12	42.13	44.69 ± 8.24	44.24
	RSA	6.44 ± 0.10	2.72	6.35 ± 0.25	4.47
Subject 3	HR	82.43 ± 2.93	3.43	85.26 ± 5.45	6.24
	RMSSD	48.41 ± 13.40	9.79	42.24 ± 8.79	13.4
	RSA	6.59 ± 0.03	7.90	6.57 ± 0.05	9.50
Subject 4	HR	92.58 ± 1.20	10.15	80.33 ± 0.41	15.20
	RMSSD	46.17 ± 2.35	10.35	30.60 ± 4.21	13.54
	RSA	6.45 ± 0.32	1.05	6.62 ± 0.26	5.04
Subject 5	HR	108.23 ± 0.23	66.65	95.39 ± 1.31	13.52
	RMSSD	17.15 ± 4.58	26.47	44.25 ± 3.53	66.54
	RSA	6.32 ± 0.12	1.01	6.47 ± 0.11	4.70

Physiological events: higher HR, lower RMSSD, and lower RSA.

In this study, we showed that with this approach is possible to measure changes in the EEG pattern during treatment elicited by interaction of the child with the therapist. An increase in relative power in Engagement compared with Disengagement emerged in the group analysis. The increase in frontal delta during cognitive tasks has been previously linked to perceptual switching of objects (Okada et al., 2009), an ability which is elicited during the imitation tasks with cubes during the imitation protocol. Occipital activity is mainly due to visual stimuli during the imitation task linked to tactile components (gamma and beta activity) (Bauer et al., 2009) and auditory component (alpha and theta) (Gladwin and de Jong, 2005). The activation of beta band within parietal regions has been linked to planning and execution of movement, although its functional role is still matter of debate (Zaepffel et al., 2013).

Interestingly, we also observed a general increase in coherence during Engagement. EEG coherence, being the covariance of spectral activity at two electrode sites, is a measure for the synchrony of neuronal activity and thus can be used as an indicator of effective cortical connectivity. Coherence mainly increased in theta, alpha and beta bands both intra- and inter-hemispheres. The increased coherence in these bands may reveal the increase of attention control during the participation in the cognitive task (Sacchet et al., 2015). Interestingly the level of coherence in frontal-parietal region in alpha band has been linked to different performances in an imitation task (Van der Helden et al., 2010). Moreover, several studies have shown a positive correlation between coherence in theta, alpha and beta and task associated with motor processing and execution (von Stein et al., 1999; Sauseng et al., 2005; Wheaton et al., 2005; Rilk et al., 2011).

A modification in asymmetry during Engagement was also observed. Previous studies have shown altered asymmetry in ASD brain both structurally and functionally. In particular, left-side prevalence in alpha and beta bands was found compared with controls both in visual and non-visual areas at rest. Right asymmetry in alpha and beta bands has been previously associated with discrimination of speech prosody (Kujala et al., 2005), processing gaze direction in face perception (Senju et al., 2005), and sustained visual attention (Stroganova et al., 2007). On the contrary, left temporal asymmetry in gamma band has been associated with language processing (Kojima et al., 2013) and an atypical asymmetry (rightward) of gamma band has been observed in ASD at rest (Maxwell et al., 2015). It seems from this study that the pattern of asymmetry shifts to the typical pattern during the Engagement phase.

It is worth noting that only two of the five subjects exhibit mu desynchronization during the imitation tasks, which could suggest a deficit in the mirror neuron system at least in some of the subjects enrolled in the study (MNS, Oberman et al., 2005). Given that all the children were able to perform the task is it possible that increase in alpha and beta coherence rather than mu desynchronization is a more reliable predictor of good performance in vasomotor tasks as suggested by Rilk et al. (2011).

ECG analysis confirmed previous findings and demonstrated that the system developed is able to detect ASD children's level of engagement (Park et al., 2013).

Some studies have shown that mental effort causes an increase in physiological arousal as measured for example by HR (Lundberg and Frankenhaeuser, 1980; Peters et al., 1998). Thus, subjective perception of mental effort may reflect changes in arousal during performance of attentive tasks. Precedent studies

demonstrated how decreased RMSSD (Nagendra et al., 2015) and RSA (Overbeek et al., 2014) represented meaningful indicators for a positive response to attention demanding stimuli and is positively associated with cognitive function, including better processing speed, working memory, learning, and receptive language skills.

The ECG features could represent a valid marker to evaluate the engagement and the social interaction of the child in real time (Moore et al., 2009).

Importantly, besides showing some common pattern of modification in physiological parameters in the enrolled subjects, the implemented protocols allowed to evidence some inter-individual differences fostering the application of this platform for a personalization of the therapeutic protocol. In particular, as regards EEG it is clearly evident that Subject 3 did not showed significant differences between Engagement and Disengagement in many cortical areas. The clinical profile of this subject shows that he has an important concentration deficit and this can explain why, despite from the behavioral observation he seemed to be engaged in the tasks proposed by the therapist as the other subjects, his brain activated differently. In addition the desynchronization of the MNS is not observed in all the subjects. If the possibility of using the proposed system for characterizing the physiological profile of specific endophenotype of ASD would be confirmed in a larger sample, it would be very useful to guide the therapist, representing a step forward in the implementation of individual therapeutic programs in ASD.

Some important issues emerged from this study that suggest future developments. First of all, the need of a standardized, objective and clear distinction of the different behaviors of each task promotes rigorous segmentation of the signals. In the future annotation of the video could be done not only with manual markers but also with automatic or semi-automatic action recognition from the video recording.

Moreover, real-time feature extraction algorithms could be implemented, which provide the therapist a feedback about the status of the child. In this way the therapist could decide to potentiate some tasks of the therapy that cause a particular engagement of the child or, on the contrary, change the therapy if the child appears to be disengaged, stressed or not interested by the task proposed.

Overall, the system presented in this study was proven to be suitable for a similar clinical scenario. The children highly accepted the monitoring platform, as demonstrated by the low dropout rate in the study and by the fact that the children included in the study did not express any discomfort/annoyance at the system. Thus, the high grade of acceptability of the monitoring platform is promising for further development and implementation of the tool. Furthermore, the smart sensorized system allowed a reliable psychophysiological characterization of the children enrolled. Such evidence fosters the applicability of the system proposed in a clinical setting, where it could be used as a smart monitoring tool to support the clinicians during the treatment. In the future the proposed system could supply useful feedback to the therapist in the treatment of ASD and even in other neurodevelopmental disabilities.

Further data collections will be needed to confirm these preliminary results. At first, larger studies would be useful to generalize the findings of this feasibility pilot study and to obtain a clearer picture of the parameters examined in ASD children. Then, when confirmed on larger cohorts, the psychophysiological characterization of the children with ASD related to different behaviors will possibly allow to personalize the treatment and to longitudinally verify the treatment effect through objective measures of brain and autonomic function of children with ASD. In conclusion, this kind of evaluation holds promise for future developments in instrumental evaluations of ASD.

Limitations

Some limitations need to be considered when interpreting the results. A first limitation is the small sample size. The study was designed as a feasibility study, thus only a small number of patients was recruited to test the applicability of the technology and the methodology.

The findings of the study need to be replicated with larger sample to prove the efficacy of the approach and the transferability in a clinical scenario. Larger sample will also allow for the evaluation of how different could be the physiological response of subgroups of children with ASD.

Another limitation is the absence of a control group, which prevents to discuss the nature of brain and autonomic response specific to ASD. In the future the comparison with a control group of age-matched children with typically development will allow to evaluate not only how different is the pattern between Engagement and Disengagement phases in ASD but also how this patterns are different from a typical pattern of response.

Finally another possible limitation is that we did not control for effects of physical movement. However, in our protocol the children were seated in a chair throughout the interaction and thus relatively restrained in their physical activity. As regards ECG, Porges et al. (2007) found that low intensity motor movements did not influence RSA or HRV in school-age children, so that movement were unlikely to have had a major impact on our results. As regards EEG we have removed muscular artifacts however visual inspection to is subjected to human error. In the future surface electromyography sensors could be used to control for children' muscular artifacts.

AUTHOR CONTRIBUTIONS

LB developed EEG algorithms and analyzed data, participated in the development of the study design, contributed in the discussion and interpretation of the results, in writing and approving the paper. AT participated in the acquisition analysis of data, contributed in the discussion and interpretation of the result, in writing and approving the paper. GT developed the ECG algorithms and contributed in writing and approving the paper. AN performed therapies and coding of videos, participated in the development of the study design, and contributed in writing and approving the paper. SP analyzed ECG data and contributed in writing and approving the paper. DC developed the ECG communication protocol and approved the paper. GB developed the ECG software data and approved

the paper. FC participated in the development of the study design, developed the video toolbox and approved the paper. SA participated in the development of technological platform and approved the paper. SC recruited the subjects and contributed in coding videos and in the discussion and interpretation of the result, in writing and approving the paper. GP participated in the development of the study design, was responsible of the technological protocol, and approved the paper. FM participated in the development of the study design, was responsible of recruitment and diagnosis of children and contributed in the discussion and approving the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2016.00276

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APPENDIX

Michelangelo Study Group

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Environmental enrichment and the sensory brain: the role of enrichment in remediating brain injury

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The brain's life-long capacity for experience-dependent plasticity allows adaptation to new environments or to changes in the environment, and to changes in internal brain states such as occurs in brain damage. Since the initial discovery by Hebb (1947) that environmental enrichment (EE) was able to confer improvements in cognitive behavior, EE has been investigated as a powerful form of experience-dependent plasticity. Animal studies have shown that exposure to EE results in a number of molecular and morphological alterations, which are thought to underpin changes in neuronal function and ultimately, behavior. These consequences of EE make it ideally suited for investigation into its use as a potential therapy after neurological disorders, such as traumatic brain injury (TBI). In this review, we aim to first briefly discuss the effects of EE on behavior and neuronal function, followed by a review of the underlying molecular and structural changes that account for EE-dependent plasticity in the normal (uninjured) adult brain. We then extend this review to specifically address the role of EE in the treatment of experimental TBI, where we will discuss the demonstrated sensorimotor and cognitive benefits associated with exposure to EE, and their possible mechanisms. Finally, we will explore the use of EE-based rehabilitation in the treatment of human TBI patients, highlighting the remaining questions regarding the effects of EE.

Keywords: EE, sensory cortices, traumatic brain injury, neuronal excitability

Experience-dependent plasticity encompasses a vast number of paradigms that range from deprivation to alterations and enrichments in the environment, and has been investigated in great detail across development through to adulthood (see reviews by Hubel and Wiesel, 1970; Hubel, 1978; Kaas, 1991; Klintsova and Greenough, 1999; Sur and Leamey, 2001; De Villers-Sidani and Merzenich, 2011; Bengoetxea et al., 2012). For the purposes of the present review, we chose to focus on plasticity conferred by global changes to the environment, termed environmental enrichment (EE). We will focus only on the changes evoked by this manipulation when applied in adulthood as our final aim is to demonstrate that it represents an exciting potential therapy in adult traumatic brain injury (TBI). As we shall review, EE alters neuronal function through a range of morphological and molecular interactions, which lead to alterations in sensorimotor and cognitive behavior. These changes make EE an ideal candidate in the treatment of TBI. To lead to this thesis, we first commence with a review of EE's capacity to evoke plasticity in the uninjured brain, to provide the context in which we will cast the role of EE in TBI. We focus here on EE-induced changes in sensory cortices due to the demonstrated effects of TBI on altering neuronal function in sensory cortices (Hall and Lifshitz, 2010; Ding et al., 2011; Alwis et al., 2012; Johnstone et al., 2013); it is also our view that changes in neuronal activity in sensory cortices after injury must underlie a significant portion of the persistent cognitive deficits found in TBI (Caeyenberghs et al., 2009; Davis and Dean, 2010; Lew et al., 2010; Folmer et al., 2011). The review of EE effects in the normal brain is also necessary to understand the mechanisms whereby EE produces changes in neuronal function in the normal brain, before we can begin to hypothesize about how EE exerts its beneficial effects after brain injury. Finally, we discuss the current literature regarding the use of EE as a potential therapy post-TBI, in animal studies with induced TBI, and in studies of human rehabilitation after injury.

WHAT IS EE?

EE refers to an experimental paradigm in which laboratory animals are housed in an environment allowing cognitive, motor and sensory stimulation at levels much greater than those which occur under standard laboratory housing conditions (Hebb, 1947, 1949; Van Praag et al., 2000). Early studies in animals have shown that the enhanced stimulation from EE produces many remarkable benefits at anatomical, molecular and behavioral levels (Hebb, 1947; Bennett et al., 1969; Diamond et al., 1972, 1976; Greenough and Volkmar, 1973; Torasdotter et al., 1998), with numerous studies following on from this work to further characterize the effects of EE (see reviews by Van Praag et al., 2000; Nithianantharajah and Hannan, 2006). In EE, the housing environment is modified by providing a larger enclosure, natural bedding and a variety of novel objects, in the expectation that this will promote greater physical activity in exploration and interaction with a novel and complex environment (Benaroya-Milshtein et al., 2004; Zebunke et al., 2013). Social enrichment in the EE environment, involving housing animals with multiple cagemates to encourage complex

social interactions (Rosenzweig et al., 1978; Mesa-Gresa et al., 2013), is also believed to contribute to an enhanced sensorimotor and cognitive experience. Enhanced physical activity and enhanced social interaction each provide benefits to the brain; physical activity on its own improves cognitive performance in parallel with a range of neural changes including enhanced neurogenesis and increased levels of neurotrophic growth factors and increased neurotransmitter subunit expression (Van Praag et al., 1999; Farmer et al., 2004; Erickson et al., 2011), while social enrichment on its own has been shown to result in an increase in brain weight (Rosenzweig et al., 1978). When the two are combined in an appropriately enriched environment, a much more extensive set of cerebral changes occurs (Rosenzweig et al., 1978; Johansson and Ohlsson, 1996; Sozda et al., 2010).

The combination of social, physical and cognitive stimulation is most often used in studies of EE and we term this "generic" EE, wherein the whole environment is non-selectively enriched. However, in some instances, in what we term "specific" EE, enrichment has been targeted to affect a specific system, e.g., auditory-specific enrichment (Engineer et al., 2004; Percaccio et al., 2005, 2007; Jakkamsetti et al., 2012) consisting of components of generic EE in combination with systems designed to produce a variety of salient sounds; or tactile-specific enrichment (Bourgeon et al., 2004; Xerri et al., 2005) where rats were raised in an environment consisting of objects with various textures. Differences in generic and specific EE will be highlighted further, in the context of EE effects on neuronal function in the cortex.

BENEFICIAL EFFECTS OF EE ON BEHAVIOR

EE exposure results in a range of sensorimotor and cognitive benefits in laboratory animals, which we only briefly summarize as these have been well reviewed elsewhere (Van Praag et al., 2000; Nithianantharajah and Hannan, 2006; Simpson and Kelly, 2011). In normal animals, EE significantly improves spatial and non-spatial learning and memory, novel object discrimination, increases the speed of spatial learning and enhances spatial searching strategies (Van Praag et al., 2000; Schrijver et al., 2002; Nithianantharajah and Hannan, 2006; Kulesskaya et al., 2011; Vedovelli et al., 2011; Leger et al., 2012). EE appears to decrease anxiety, as evidenced in a variety of tests (Fernandez-Teruel et al., 2002; Larsson et al., 2002; Galani et al., 2007; Harati et al., 2013). EE also improves task-learning, and recent and remote memory retrieval (Harati et al., 2013), likely due to a greater ability to consolidate and retain information because of social enrichment (Gardner et al., 1975). However, effects are not all positive and studies have shown both increases and decreases in aggressive social behavior after EE (Abou-Ismail, 2011; Workman et al., 2011; McQuaid et al., 2012; Mesa-Gresa et al., 2013), possibly due to factors such as differences in EE housing conditions, strain differences, and experimental design.

In a similar vein, the consensus (Nithianantharajah and Hannan, 2006; Kazlauckas et al., 2011; Landers et al., 2011) is that EE encourages activity and exploratory behavior though there are some inconsistencies: some studies show increased activity in novel environments (Benaroya-Milshtein et al., 2004), and others show faster habituation and less activity (Zimmermann et al., 2001; Schrijver et al., 2002; Elliott and Grunberg, 2005), when compared with animals housed in standard or impoverished environments (Varty et al., 2000; Zimmermann et al., 2001). Recently, Zebunke et al. (2013) showed a decrease in general activity during an open field test, with an increase in duration of exploration of novel objects by pigs exposed to cognitive enrichment. Similarly, Mesa-Gresa et al. (2013) also found that EE rats exhibited longer durations of novel object exploration, while Schrijver et al. (2002) found an increase in activity in a light/dark box in EE rats. Bruel-Jungerman et al. (2005) have also reported that EE animals were capable of retaining memory during a novel object recognition test for up to 48 h after initial exposure, despite a lower object exploration time during the learning phase of the test.

Among the most robust of findings is that EE and sensory training/learning improves stimulus discrimination (Gibson, 1953; Kendrick et al., 1992; Recanzone et al., 1993). Mandairon et al. (2006a,b) have shown that olfactory enrichment results in an improved ability to discriminate between odor pairs, likely due to changes in neuronal response properties (Buonviso and Chaput, 2000; Fletcher and Wilson, 2003). Similarly, EE enhances spatial discrimination of sound source, with faster reaction times and improved discrimination accuracy (Cai et al., 2009). Bourgeon et al. (2004) reported that while EE housing did not affect an animal's tactile ability to discriminate between textured surfaces, enriched animals did learn to perform the discrimination task faster. The changes in behavior reported above must occur as a consequence of the effects of EE on neuronal function, which in turn, occur as a result of the various molecular and morphological changes mediated by EE.

NEURONAL FUNCTIONAL CHANGES ASSOCIATED WITH EXPOSURE TO EE

The EE-induced changes in behavior can be linked to specific changes in neuronal functionality. This has been studied in best detail for behavior associated with hippocampal function (Van Praag et al., 2000; Eckert and Abraham, 2013) and we briefly describe these as a prelude to describing the changes seen in adult sensory cortices, the particular brain regions of interest here in the context of our over-arching thesis (Alwis et al., 2012) that many persistent cognitive and motor deficits in TBI have sensory deficits as an underlying cause. The studies discussed below have used electrophysiological techniques such as *in vivo* and *in vitro* intra and extracellular recordings to specifically investigate EE-induced changes in neuronal function.

EE-induced improvements in hippocampal-dependent memory function have been linked to experience-dependent changes in hippocampal synaptic strength (Kempermann et al., 1997; Schrijver et al., 2002; Vedovelli et al., 2011), with reports of increases in excitatory post-synaptic potential (EPSP) amplitudes and evoked population spikes in rats exposed to generic EE, both in *in vivo* studies (Sharp et al., 1985; Irvine and Abraham, 2005; Irvine et al., 2006) and in *in vitro* studies of slices from the dentate gyrus (Green and Greenough, 1986; Foster et al., 1996) or the CA3-CA1 pathway (Foster and Dumas, 2001; Malik and Chattarji, 2012). The enhanced synaptic efficacy in dentate gyrus appears likely to act through AMPA and NMDA receptor mediated mechanisms (Foster et al., 1996). Interestingly, these increases did not outlast the termination of EE housing

(Green and Greenough, 1986), even though EE-induced changes in behavior and morphology persist after discontinuation of EE (Camel et al., 1986; Cheng et al., 2012), suggesting that information stored in the dentate gyrus may be related to more transient behavioral effects of EE. However, there is also contradiction in studies of EE-induced long-term hippocampal plasticity. Eckert and Abraham (2010) reported that long-term exposure to EE did not result in enhanced synaptic transmission in the hippocampus, both *in vivo* and *in vitro*, suggesting that the variability in these studies may have be due to different EE paradigms, or to homeostatic mechanisms to re-establish normal synaptic transmission (Turrigiano, 1999, 2008). Foster and colleagues (Foster et al., 1996; Foster and Dumas, 2001) demonstrated that EE housing inhibits LTP induction in the perforant pathway, suggesting that both experience-dependent synaptic plasticity and LTP expression share similar yet-unknown underlying mechanisms. Conversely, increased LTP expression has been reported after EE exposure (Duffy et al., 2001; Artola et al., 2006; Eckert and Abraham, 2010; Malik and Chattarji, 2012). One resolution for these effects, other than differences in the EE conditions, is that LTP induction after EE may be differentially regulated in different regions of the hippocampus.

It is worth noting here that short-term plasticity in the hippocampus has not been shown to be affected by EE (Foster et al., 1996; Foster and Dumas, 2001; Eckert and Abraham, 2010; Malik and Chattarji, 2012).

In contrast to the hippocampus, little is known about EE-induced changes in neuronal functionality in cortex. What changes there are in cortical neuronal function have mainly been examined at the level of the sensory cortices and we discuss these studies in detail below. EE-induced changes in neuronal function in the normal (uninjured) sensory cortices are particularly salient to our thesis and may provide us with insights into the role of EE on neuronal function after brain injury, of which nothing is known as yet.

EE AND SENSORY CORTICES

The effects of EE have been studied most extensively in auditory cortex, in some detail in somatosensory cortex, and only to a limited degree in visual cortex.

In auditory cortex, the effect of EE has been studied at levels ranging from brain slices through to extracellular recordings from neurons in anaesthetized animals. In the investigation of the effects of EE on the auditory cortex, studies have used enriched environments that include specific auditory enrichment in the form of playback of various sounds within the housing environment (Engineer et al., 2004; Percaccio et al., 2005, 2007; Nichols et al., 2007). Many studies report effects that mirror those seen in the hippocampus, of increased synaptic efficiency. Thus, auditory cortex slices show that specific EE induces an increase in excitatory post-synaptic current (EPSC) amplitudes, coupled with a decrease in current rise-times in supragranular cortical layers and no changes in infragranular layer V (Nichols et al., 2007). *In vivo* recordings from the anaesthetized rat, primarily from Layers 4/5 of adult primary auditory cortex after specific auditory EE, have demonstrated an increase in cortical responsiveness (both spontaneous and stimulus-evoked), decreased response latencies, and an increase in frequency selectivity (Engineer et al., 2004; Percaccio et al., 2005; Cai et al., 2009). Percaccio et al. (2005, 2007) also found that EE increased paired pulse depression (PPD) in the rat auditory cortex, indicating an increased probability of synaptic transmitter release and thus, enhanced synaptic transmission. Other studies in auditory cortex found EE could cause reorganization of the cortical tonotopic map (Norena et al., 2006; Pienkowski and Eggermont, 2009; Zhou et al., 2011; Kim and Bao, 2013), and alterations in stimulus frequency selectivity over either a range of frequencies (Zhou et al., 2011) or for frequencies specific to those used as a part of the enrichment condition (Norena et al., 2006; Pienkowski and Eggermont, 2009).

The effects of auditory enrichment are not restricted to primary auditory cortex, and Jakkamsetti et al. (2012) have reported that responses in posterior auditory field (PAF) are also increased when compared with animals housed in standard environments. These increased firing rates were accompanied by decreases in response latency and duration, and a reduction in receptive field size, as seen in primary auditory cortex (Engineer et al., 2004; Zhou et al., 2011; Jakkamsetti et al., 2012).

Unlike the above-noted reports, some studies do not report increased neuronal responsiveness and sharper frequency tuning after exposure to auditory enrichment (Condon and Weinberger, 1991; Bao et al., 2003). Instead, these studies found that a repeated auditory stimulus decreased responsiveness to frequencies used in the stimulus (Condon and Weinberger, 1991), and exposure to noise burst trains produced broadly tuned receptive fields (Bao et al., 2003). Percaccio et al. (2007) have suggested that a critical variable in eliciting EE effects in auditory cortex is the nature of the enrichment, i.e., how engaging or complex the stimuli are. This would explain the increased neuronal responsiveness reported by Percaccio et al. (2007) in rats receiving even passive exposure to specific auditory EE, which included situation-dependent stimuli from the environment and from cagemates, as opposed to simple, less behaviorally relevant stimuli.

Similar to studies in auditory cortex, generic EE (i.e., non-specific enrichment) results in reorganized cortical topographic maps, decreased receptive field sizes, increased response selectivity and increased sensory evoked potentials in the somatosensory cortex (Xerri et al., 1996; Coq and Xerri, 1998; Polley et al., 2004; Devonshire et al., 2010). One interesting effect demonstrated here is that EE effects on receptive field sizes and responses to stimulation of the main topographic input to the neurons may be laminar selective (an effect that does not appear to have been explored in auditory cortex). Thus, in the rodent barrel cortex that receives tactile input from the mystacial whiskers, EE caused a decrease in receptive field size and in neuronal responses evoked by stimulation of the "Principal Whisker" (the topographically matched whisker providing the main input to a group of neurons in the barrel cortex) in supragranular cortical Layers 2/3, but there were no changes in response strength or receptive field size in input Layer 4 (Polley et al., 2004). It is worth noting that Guic et al. (2008) found that EE caused an increase in cortical representational area in Layer 4. However, these effects were seen after stimulation of only a few selective whiskers, while other whiskers were trimmed whereas Polley et al. (2004) used a non-deprived paradigm where all whiskers remained untrimmed.

These different effects are likely a reflection of variations in experimental design of the EE conditions, consistent with the conclusions drawn from studies in auditory cortex that the nature of EE conditions influences neuronal outcomes.

These studies, where the emphasis was on measuring receptive field sizes and responses only to simple input from the main topographically-matched region of the body, indicated laminar specificity of effects. However, when neuronal encoding of sophisticated sensory input is the metric, the effects of generic EE occur globally across all cortical layers. Thus, in our own studies, 8–10 weeks of EE exposure increased neuronal firing rates globally across all layers 2–5 of the rat barrel cortex, and did so in response to both simple stimuli and a variety of complex, naturalistic stimuli (Alwis and Rajan, 2013). It is interesting to note that these effects occur even to the complex stimuli as our previous work on TBI (Alwis et al., 2012) had suggested that the complex stimuli may engage a diversity of intra-cortical processing mechanisms not seen with the simple stimuli. These effects occurred without any change in response latency, suggesting that the effects were specific to cortex and not due to changes at lower levels of the somatic pathways to cortex.

Although not often studied on its own in somatosensory cortex, recently EE has been combined with another manipulation that induces experience-dependent plasticity in barrel cortex, viz. whisker trimming and/or stimulation (Armstrong-James et al., 1992; Diamond et al., 1993, 1994; Rema et al., 2006; Guic et al., 2008; Megevand et al., 2009). Here the picture is rather murky, with one study suggesting that EE operates through different mechanisms than other plasticity mechanisms in barrel cortex, but another suggesting that it operates through the same mechanisms. The first seems to apply in the case of whisker trimming: when whisker pairing (all whiskers on one side of the face trimmed except for a pair of adjacent whiskers) is coupled with short (15 h) generic EE exposure, there is an accentuation of the effects induced by whisker trimming alone: a faster shift of receptive field bias toward the untrimmed whiskers, stronger evoked responses to the intact paired whisker than to deprived whiskers, and increased spontaneous activity in supra-granular and granular layers (Rema et al., 2006). In contrast EE may operate through the same mechanisms as some other plasticity cases. Thus, a short duration of whisker stimulation at a frequency often used during exploratory whisking behavior increases stimulus evoked potentials in both supra-granular and granular barrel cortex layers (Megevand et al., 2009)—but, addition of EE to the whisker stimulation paradigm does *not* further potentiate responses (Megevand et al., 2009).

Finally, only a limited number of studies have examined the effects of EE in the normal visual cortex. In area 17 of the adult visual cortex, similar to effects seen in the auditory cortex, generic EE results in sharper bandwidths in orientation tuned cells, increased neuronal responses to light stimuli, increased visual acuity, as well as increased stimulus contrast and temporal selectivity (Beaulieu and Cynader, 1990a,b; Mainardi et al., 2010). In addition to these effects in normal adult visual cortex, studies of EE-induced plasticity in the adult visual cortex have also examined effects in the context of monocular deprivation (MD) and amblyopia. MD during developmentally critical periods induces a shift in ocular dominance (OD) so that more neurons respond to stimulation of the open eye (Frenkel and Bear, 2004; Mrsic-Flogel et al., 2007). Such plasticity is normally not seen when MD is started in adulthood, but EE housing for 3 weeks reactivates cortical plasticity in supragranular layers of adult visual cortex such that OD changes are possible again and visual evoked potentials (VEPs) elicited by stimulation of the deprived eye are greatly depressed (Baroncelli et al., 2010b). In amblyopia, individual components of EE such as motor and visual stimulation, as well as the combination of these components, also recover visual acuity and restore OD plasticity and binocularity in supragranular layers of adult visual cortex (Sale et al., 2007; Baroncelli et al., 2012; Tognini et al., 2012).

Taken together, these studies of EE effects in sensory cortices show that generic EE is potent at producing many changes in neuronal responses, such as stronger responses and greater stimulus selectivity; that the receptive field effects may be laminar-selective and depend on the type of enrichment but that effects on more sophisticated neuronal processing, particularly of naturalistic stimuli that mimic everyday events, occur across all cortical laminae; and finally, that EE may operate independent of some other mechanisms of cortical plasticity.

MECHANISMS UNDERLYING EE-INDUCED CHANGES IN NEURONAL FUNCTION

There are numerous well-documented structural and biochemical consequences of EE which may underlie the effects of EE on neuronal function. We broadly review these changes with EE (summarized in **Figure 1**). It must be noted that in most cases, we do not know how these structural and molecular changes contribute to EE-induced changes in neuronal function: to date, there has been very limited attempt only to directly manipulate these fine-scale changes to determine to what extent they cause EE-related changes in neuronal functionality.

MORPHOLOGICAL CHANGES

It was very early recognized that exposure to complex, enriched environments causes gross morphological changes in an overall increase in brain weight, particularly in cortical and hippocampal weight and thickness (Bennett et al., 1969; Walsh et al., 1969; Diamond et al., 1972, 1976). The factors contributing to these gross morphological changes include increased neuronal density and size, increased dendritic branching and length, increased dendritic spine density, and increased turnover in pyramidal and stellate cells (Holloway, 1966; Diamond et al., 1967; Volkmar and Greenough, 1972; Globus et al., 1973; Greenough and Volkmar, 1973; Greenough et al., 1973; Uylings et al., 1978; Connor et al., 1982; Turner and Greenough, 1985; Kempermann et al., 1997; Leggio et al., 2005; Jung and Herms, 2012). Unsurprisingly, the changes in dendritic morphology are accompanied by synaptic alterations, with EE resulting in increased numbers of synapses and synaptic contacts (Jones et al., 1997; Briones et al., 2004; Landers et al., 2011), which could enhance cortical synaptic transmission and hence, alter cortical excitation/inhibition balances.

One particularly notable EE-induced change is neurogenesis, which may contribute to enhanced cognitive performance

Morphological effects
• ↑ dendritic branching, length
• ↑ dendritic spine density, neuronal density, synaptic density
• ↑ neurogenesis
• ↑ cell survival

Molecular effects
• ↑ neurotrophic factor expression
• ↑ neurotransmitter levels
• ↑ neurotransmitter receptor expression
• ↑ synaptic protein expression

FIGURE 1 | Environmental enrichment induces morphological and molecular changes in the brain. An overview of the number of structural and molecular mechanisms that contribute to the changes in neuronal function, and ultimately, changes in behavior, seen after EE exposure. These mechanisms are thought to underlie EE-induced neural plasticity.

(Kempermann et al., 1997, 1998; Nilsson et al., 1999; Bruel-Jungerman et al., 2005). Cell proliferation, improved neuronal survival and functional integration of new neurons have all been demonstrated to occur in the adult dentate gyrus after EE (Kempermann et al., 1997, 1998; Van Praag et al., 2000; Lu et al., 2003; Bruel-Jungerman et al., 2005) and pharmacological inhibition of cell proliferation during EE prevented hippocampal neurogenesis and any improvement in a hippocampal-based memory task (Bruel-Jungerman et al., 2005). Decreased neurogenesis has been linked to cognitive decline (Drapeau et al., 2003, 2007), and restoration of neuronal proliferation and survival leads to an improvement in cognitive behavior (Kempermann, 2002).

The enhanced hippocampal neurogenesis, improved neuronal cell survival, increased synaptic density and dendritic branching (Kempermann et al., 1997, 1998; Bruel-Jungerman et al., 2005), and the growth factor up-regulation that is discussed below, have all been suggested to be responsible for EE-induced improvements in spatial and non-spatial learning and memory and enhanced spatial searching strategies (Van Praag et al., 2000; Schrijver et al., 2002; Nithianantharajah and Hannan, 2006; Kulesskaya et al., 2011; Vedovelli et al., 2011; Leger et al., 2012). Increased habituation to novel objects has also been attributed to a decrease in activation of hippocampal neurons during novel object exposure in enriched animals, in contrast to the increased activation seen in animals housed in standard conditions when exposed to objects in novel environments (Zhu et al., 1997; Leger et al., 2012). These results support the idea that EE-induced morphological changes contribute to alterations in behavior, through changes in overall neuronal function.

It must be noted here that similar neurogenesis has not been demonstrated to occur in cortex after EE, but this may be for a want of study not for an absence of the effect. In the absence of this effect, it is difficult to speculate to what extent neurogenesis contributes to EE-induced changes in cortical neuronal functionality or cortex-based processes. We will argue below that, in any case, neurogenesis is not required to occur in cortex to produce the EE-induced changes in responses and in functionality and that those changes can be produced by alterations in the balance between excitation/inhibition interplay that shapes neuronal responses and function.

MOLECULAR CHANGES

The EE-induced structural and functional changes described above occur through molecular cascades that involve increases in neurotrophic factor and neurotransmitter levels (Van Praag et al., 2000; Mohammed et al., 2002; Will et al., 2004; Nithianantharajah and Hannan, 2006), and increased expression of regulatory proteins that enhance the number and stability of synapses, increase cell proliferation, and promote neurotransmitter release (Rampon et al., 2000; Frick and Fernandez, 2003; Nithianantharajah et al., 2004).

Neurotrophic factors of particular importance to EE include brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), with levels of both increasing following exposure to exercise and EE (Pham et al., 1999; Birch et al., 2013) in brain regions including cortex, hippocampus and cerebellum (Torasdotter et al., 1998; Angelucci et al., 2009). In the adult brain, BDNF and NGF promote experience-dependent plasticity by enhancing synaptic plasticity, signaling, learning and memory (Kang and Schuman, 1995; Torasdotter et al., 1998; Pham et al., 1999; Bekinschtein et al., 2011). Increases in neurotrophins appear to underlie improved motor and cognitive function after EE (Falkenberg et al., 1992; Henriksson et al., 1992; Linnarsson et al., 1997; Bekinschtein et al., 2011; Gelfo et al., 2011; Bechara and Kelly, 2013; Birch et al., 2013) since suppression of BDNF levels causes deficits in neurogenesis, learning behavior and memory (Linnarsson et al., 1997; Minichiello et al., 1999; Rossi et al., 2006; Heldt et al., 2007; Furini et al., 2010).

Similarly, neurotransmitter levels are also affected by exposure to EE, suggesting a role in the mediation of brain plasticity. Serotonin is important in promoting neuroplasticity (Maya Vetencourt et al., 2008; Baroncelli et al., 2010a), and EE induces an increase in serotonin receptor expression and in serotonin levels (Rasmuson et al., 1998; Koh et al., 2007; Baroncelli et al., 2010a). Levels of other neurotransmitters associated with synaptic plasticity, such as acetylcholine and noradrenaline, also increase following EE (Por et al., 1982; Galani et al., 2007; Brenes et al., 2009). Increased cortical responsiveness may then be attributed to increases in synaptic transmission efficacy and synaptic strength (Mainardi et al., 2010) brought about by EE-induced molecular changes.

In conjunction with these changes in neurotransmitter levels, excitatory activity also shifts following EE housing, with increases in hippocampal extracellular glutamate levels coupled with an enhanced expression of AMPA and NMDA receptors (Tang et al., 2001; Naka et al., 2005; Segovia et al., 2006). Changes in hippocampal field potentials have been attributed to factors that include increased AMPA receptor-mediated transmitter binding, increased expression of AMPA and NMDA receptor subunits, increased dendritic spine density and upregulation of growth factors (Sharp et al., 1985; Green and Greenough, 1986; Foster and Dumas, 2001; Eckert and Abraham, 2010). There is also evidence of synaptic plasticity, in the form of increased dentate gyrus LTP, in the hippocampus after physical activity, which is an important component of the EE experience (Van Praag et al., 1999). The role of these changes in excitation will be discussed in greater detail below where we argue that a principal mechanism through which EE alters brain function and behavior is by promoting a shift toward excitation in neuronal responses.

ROLE OF CHANGES IN CORTICAL EXCITATION/INHIBITION BALANCE IN EE-INDUCED CHANGES IN NEURONAL FUNCTIONALITY

As shown above, EE-induced brain plasticity is likely to occur through the combination of structural and biochemical changes that can impact on neuronal functionality. We believe that there is substantive evidence that one particularly important end-effect through which EE alters neuronal function is alterations in the balance between excitation and inhibition in cortex (Engineer et al., 2004; Percaccio et al., 2005, 2007). This E/I balance is a critical factor in regulating cortical neuronal functionality and critical periods of cortical plasticity which occur throughout development are governed by this E/I balance (Hensch and Fagiolini, 2005; Levelt and Hubener, 2012) whereby immaturity of cortical inhibition promotes plasticity while maturation of inhibitory circuits results in the decrease in plasticity associated with cortical maturation (Huang et al., 1999; Fagiolini and Hensch, 2000). Shifts in this E/I balance may also play a major role in the experience-dependent cortical plasticity, which includes plasticity induced by EE or deprivation, that occurs outside developmental critical periods (Hensch and Fagiolini, 2005; Sale et al., 2007; Benali et al., 2008; Maya Vetencourt et al., 2008; Megevand et al., 2009; Baroncelli et al., 2010b, 2011; Luz and Shamir, 2012; Maya-Vetencourt et al., 2012). Changes in neuronal function in the adult brain suggest that EE exposure causes a reactivation of forms of neuronal plasticity generally seen only in the developing, immature brain (Chang and Merzenich, 2003; Chang et al., 2005) in which inhibitory mechanisms are immature.

Experience-dependent changes in response strength and sensitivity in adult sensory cortices have been attributed to decreased levels of cortical inhibition (Buonomano and Merzenich, 1998; Baroncelli et al., 2011), which shift cortical E/I ratios to favor excitation. Studies have demonstrated the importance of GABA synthesis in promoting plasticity (Hensch et al., 1998; Harauzov et al., 2010) after MD, and disruption of GABA-ergic inhibition through pharmacological treatments or EE reinstates plasticity to restore OD plasticity in adult visual cortex (Sale et al., 2007; Maya Vetencourt et al., 2008; Harauzov et al., 2010; Zhou et al., 2011; Maya-Vetencourt et al., 2012). Similarly, Zhou et al. (2011) found that EE-induced plasticity in auditory cortex was accompanied by a decrease in GABA receptor subunit expression. Sale et al. (2007) have also shown that EE exposure results in a decrease in basal extracellular GABA levels in the visual cortex, and that EE-induced plasticity can be countered by pharmacologically increasing inhibitory activity. EE-induced decreases in cortical inhibition have been demonstrated in studies of auditory and visual cortex, through decreases in GABA receptor subunit expression, inhibitory synapse density and basal levels of GABA (Beaulieu and Colonnier, 1987; Zhou et al., 2011; Jakkamsetti et al., 2012), while GAD67 expression has also been shown to decrease following exposure to EE (Scali et al., 2012; Tognini et al., 2012).

However, decreased inhibition may just be one mechanism underlying EE-induced plasticity via shifts in the excitation/inhibition balance, with studies also suggesting an increase in cortical excitation with EE. Nichols et al. (2007) have shown that exposure to EE induces an AMPA-receptor mediated increase in EPSC amplitudes in supragranular layers of the auditory cortex, with no changes in GABA-ergic transmission, while the increase in PPD after EE demonstrated by Percaccio et al. (2005) suggests an increase in the transmitter release probability of excitatory synapses.

Taken together, the results presented in this section suggest that EE exerts its effects through molecular changes, which in turn support changes in morphology and neuronal function. These results also suggest that in conditions such as brain injury, which result in abnormal neuronal activity, EE-induced plasticity may have the potential as a therapy to steer neuronal activity toward a more functionally relevant state. This is particularly the case when it is considered that excitation/inhibition shifts may also occur in brain injury (Ding et al., 2008; Alwis et al., 2012; Johnstone et al., 2013).

EE AND THE DAMAGED BRAIN

Considering that the brain plasticity evoked by EE results in various behavioral benefits, it is hardly surprising that EE (and specifically the form we have termed "generic" EE) has been proposed as a putative therapy for neurological conditions ranging from Alzheimer's disease through to ischemia/stroke (Faherty et al., 2005; Jadavji et al., 2006; Buchhold et al., 2007; Nithianantharajah et al., 2008; Wang et al., 2008; Hu et al., 2010; Valero et al., 2011; Du et al., 2012). Indeed, EE ameliorates the behavioral and pathological deficits associated with many of these conditions:

for example, in models of Alzheimer's disease, EE enhances neuronal proliferation, survival and maturation, leading to improved cognition (Hu et al., 2010; Valero et al., 2011), while in studies of stroke/ischemia, EE improves sensorimotor function, such as impaired gait and limb placement (Buchhold et al., 2007; Wang et al., 2008).

Our focus in this review is on the potential role of EE as a therapy for TBI, based on its known effects on brain changes induced by TBI, especially in the sensory cortices. For this consideration, it is necessary to first define some of the basic features of TBI and its effects on brain and behavior. There are two major forms of TBI—focal and diffuse. Focal brain injury is caused by direct, localized damage to the brain, while diffuse injury is most commonly caused by indirect forces, such as during rapid acceleration/deceleration of the head (Andriessen et al., 2010; Alwis et al., 2013). TBI affects approximately 2 million individuals every year in the US alone (Faul et al., 2010) and has been shown to result in a number of persistent sensory deficits, which are thought to underlie TBI-associated cognitive disabilities (Caeyenberghs et al., 2009; Davis and Dean, 2010; Lew et al., 2010; Folmer et al., 2011). People with mild to moderate diffuse TBI usually recover motor skills fully, but have other prolonged deficits, including cognitive deficits and memory loss, likely from axonal injury (Strich, 1956; Adams et al., 1999; Graham et al., 2000; Little et al., 2010).

In TBI there are often substantial and prolonged functional deficits in cognition, memory and movement (Gagnon et al., 1998; Draper and Ponsford, 2008; Park et al., 2008; Faul et al., 2010; Risdall and Menon, 2011) and these are invariably viewed as resulting from damage to brain areas specific to those functions. What has been consistently overlooked is that most TBI sufferers show deficits in how they process sensory information. What we see, hear, touch is used to understand the world and guide complex behaviors like thinking, movement, or memory; sensory processing deficits easily affect these behaviors. It has been recognized that at least some impairments may involve disruption of the integration of sensory input (Brosseau-Lachaine et al., 2008; Patel et al., 2011). In humans, speeded motor tasks and response time tasks are also affected in mild/moderate TBI (Bawden et al., 1985; Haaland et al., 1994), and animal studies have shown persistent abnormal sensory behavior (McNamara et al., 2010), again suggesting disturbances in sensorimotor processing, and there are many long-lasting sensory and cognitive impairments even after motor function has recovered (Narayan et al., 2002; Draper and Ponsford, 2009; Faul et al., 2010; Risdall and Menon, 2011).

Consistent with this hypothesis of a sensory cortices basis for persistent cognitive, memory and motor deficits in TBI, experimental TBI causes significant time-dependent changes in neuronal excitability in sensory cortices (Hall and Lifshitz, 2010; Ding et al., 2011; Alwis et al., 2012). In the immediate post-TBI period, changes in neuronal activity occur across all cortical layers, and consist in a depth-dependent (from the cortical surface) suppression of responses to all types of simple and complex naturalistic stimuli (Johnstone et al., 2013; Yan et al., 2013). However, by the long-term (8–10 weeks post-TBI), effects are found only in the upper cortical layers, layers 2 and upper layer 3, and decrease with cortical depth such that there are no long-term changes in input layer 4 (Alwis et al., 2012); further the changes in the upper layers are no longer a suppression of responses but, rather, a hyper-excitation (Alwis et al., 2012). These persistent effects are consistent with an imbalance in cortical excitation/inhibition (Ding et al., 2011; Alwis et al., 2012).

Given the known effects of EE on the E/I balance in cortex, we believe that there is potential for EE to remediate TBI-induced changes in neuronal function by restoring the cortical excitation/inhibition balance, to improve sensorimotor and cognitive behavior. However, there is no current literature probing the effects of EE specifically on neuronal function post-TBI, highlighting the need for studies examining the mechanisms underlying the EE-induced functional improvements that have been reported in the literature. Hence, in the following section of the review, we will first consolidate and discuss studies that have examined the effects of EE after experimental brain injury, which have focussed on mainly behavioral effects. We will then discuss possible mechanisms through which EE acts to improve functional outcomes post-injury, based on the known mechanisms underlying the effects of EE (as discussed above). Finally, we will review the implementation and efficacy of EE as a therapeutic option to remediate brain injury in a clinical setting.

THE BENEFICIAL EFFECTS OF EE POST-TBI

Only a few studies have investigated the effects of EE on functional recovery post-experimental TBI and shown that exposure to EE ameliorates motor and cognitive deficits and TBI-induced histopathologies (Hamm et al., 1996; Passineau et al., 2001; Hicks et al., 2002; Sozda et al., 2010; De Witt et al., 2011; Matter et al., 2011; Monaco et al., 2013; Bondi et al., 2014), with some very limited work on the effect of EE on TBI-induced sensory morbidities. These studies have predominantly studied the use of generic EE in the treatment of TBI, except for some work that has included the use of multi-modal sensory stimulation with generic EE (discussed further below).

EE improves TBI-induced cellular histopathologies: EE-treated animals show decreases in lesion volume, increased neuronal survival, and reduced neuronal degeneration in cortex (Passineau et al., 2001; Lippert-Gruner et al., 2007; Monaco et al., 2013). Muthuraju et al. (2012) recently reported an EE-mediated decrease in cell death, in conjunction with an increase in neurogenesis in the striatum, post-TBI. Additionally, in correlation with the positive effects on motor and cognitive function, decreased apoptosis and lesion volume have also been shown using a combination of multi-modal sensory stimulation and EE (Maegele et al., 2005a; Lippert-Gruner et al., 2007). These effects suggest that EE may be able to ameliorate or attenuate damage caused by secondary injury processes, which are often complex and dynamic in nature.

The effects of EE on motor and cognitive function after TBI have only been investigated in TBI models that cause a mixture of focal and diffuse TBI (Hamm et al., 1996; Passineau et al., 2001; Hicks et al., 2002; Hoffman et al., 2008; Sozda et al., 2010; De Witt et al., 2011; Matter et al., 2011; Monaco et al., 2013), and to date, no studies have examined the effect of EE after a purely diffuse model of TBI. The studies of EE effects in mixed model TBI have demonstrated positive effects of EE on neuromotor and cognitive

function, especially for spatial navigation and memory. Hamm et al. (1996) found that at 11–15 days after mixed-model TBI, animals exposed to generic EE displayed elevated spatial memory function in the Morris Water Maze (MWM) test, when compared with TBI animals housed in standard conditions. EE housing also improved cognitive functioning to levels comparable to those of sham controls (Hamm et al., 1996). These findings are similar to reports demonstrating EE-induced recovery of spatial navigation and spatial memory after hippocampal/cortical lesions (Will et al., 1977; Einon et al., 1980; Whishaw et al., 1984). EE-induced improvements in spatial navigation, increases in spatial acquisition task rate, as well as improved spatial memory, have been demonstrated in other experimental models of mixed-model TBI (Passineau et al., 2001; Hicks et al., 2002; Wagner et al., 2002; De Witt et al., 2011; Matter et al., 2011; Monaco et al., 2013). EE-mediated recovery of locomotor activity and motor function in beam-walking and rotatod tasks has also been documented post-TBI (Wagner et al., 2002; De Witt et al., 2011; Matter et al., 2011; Monaco et al., 2013), while EE exposure also improved recovery time of forelimb function after CCI (controlled cortical impact) injury (Smith et al., 2007).

While EE on its own has all of these benefits for motor and cognitive function, there is also evidence that the use of additional multi-modal sensorimotor stimulation together with EE can improve cognitive and motor function (Maegele et al., 2005b; Lippert-Gruener et al., 2007; Lippert-Gruner et al., 2007, 2011) at both acute (7 and 15d; Maegele et al., 2005a,b; Lippert-Gruner et al., 2007), and chronic (30d; Lippert-Gruener et al., 2007) time-points post-injury. Such enhanced stimulation is thought to better mimic rehabilitation paradigms used in clinical settings in the treatment of brain injury. Maegele et al. (2005a) have demonstrated that enhanced sensory stimulation in combination with EE improves behavioral outcomes more than the use of EE on its own (Maegele et al., 2005a), suggesting that any neuroplasticity conferred by increased stimulation may be therapeutically relevant.

Only a very few studies have examined the efficacy of EE in ameliorating sensory deficits after TBI, with only one study (Johnson et al., 2013) reporting that EE exposure completely recovers TBI-induced sensory neglect, a condition where there is a reduction in responsiveness to sensorimotor stimuli (Kim et al., 1999). Conversely, in a unilateral cortical lesion model of brain injury, Rose et al. (1987) found that EE did not facilitate recovery from sensory neglect post-lesion. These contradictory results may be explained by differences in the nature of injury, or even the timing of EE exposure: in the Johnson et al. (2013) study, 15 days of EE exposure occurred immediately *prior* to TBI, whilst Rose et al. (1987) examined the effects of 6 weeks of EE exposure commencing 10–12 days post-lesion. We will demonstrate below that the timing of the application of EE is absolutely critical for ameliorating TBI-induced behavior deficits.

In most of these studies, the type of EE applied has been what we have termed "generic" EE. Whether fortuitous or planned, this form of EE, which must engage a range of sensory, motor, cognitive and social behaviors, appears to greatly improve recovery post-TBI. Thus, Hoffman et al. (2008) indicate that EE-induced functional recovery may depend on task-specific experience: post-TBI, animals show enhanced recovery of motor function (e.g., beam traversing and balancing) and spatial learning and memory (decreased latency to locate a platform in the MWM), when exposed to both EE *and* task-specific training for the motor and cognitive tests. They also suggest that the enhanced motor, social and cognitive stimulation provided by housing in EE conditions could, in themselves, contribute to the improved motor and cognitive they observed. It is possible that exposure to general EE vs. specific EE dictates the level of functionality that is conferred; although it is true that often studies using specific EE focus on tasks related to the aspect of EE that they enhance. Considering the ambiguity that remains concerning this issue, further investigations are required to determine whether exposure to task-specific experience or specific EE can improve overall functionality in a range of tasks.

It has been suggested that improved sensorimotor function after brain injury may actually be attributed to behavioral compensation rather than functional recovery; improvements on multi-sensory tasks, such as a MWM test, could be due to the use of cues from alternate (presumably undamaged) modalities (Finger, 1978; Rose et al., 1987, 1993; Kolb et al., 1996). This view receives support from studies that show that EE has much more limited or negligible benefit in tasks involving a single sensory modality (Rose et al., 1987, 1988). However, there is also no reason why the two effects could not o-exist and in keeping with this possibility, studies have shown a degree of EE-induced functional recovery after cortical injury, accompanied by an observed difference in the movements of the animals during task performance such as skilled reaching post-injury (Whishaw et al., 1991; Rowntree and Kolb, 1997; Kolb, 1999), suggesting that perhaps both recovery and compensation may account for improved functional outcomes after injury, possibly through the recruitment of uninjured cortical circuits (Kolb, 1999). We therefore turn now to a consideration of the potential mechanisms whereby EE could improve outcomes after TBI.

MECHANISMS PROMOTING IMPROVED BEHAVIORAL AND PATHOLOGICAL RECOVERY

To understand how EE could promote recovery after TBI, it is necessary to understand some of the mechanisms underlying TBI. This is not a simple endeavor since neurodegeneration caused by TBI occurs as a result of a number of complex and dynamic inter-related mechanisms (Smith et al., 1991; Hicks et al., 1993; Pierce et al., 1998; Hall and Lifshitz, 2010; McNamara et al., 2010). Only a few studies have examined how EE impacts on these complex molecular and anatomical factors affected in TBI or any other form of brain injury. Thus, ideas of how EE might produce improvements in sensorimotor and cognitive behavior after TBI or any brain injury are often based on extrapolations of the known actions of EE in the normal brain.

In uninjured animals, EE enhances neurogenesis, improves neuronal survival, and decreases apoptotic cell death (Kempermann et al., 1997; Van Praag et al., 2000; Lu et al., 2003; Bruel-Jungerman et al., 2005), all of which have been linked to improved behavioral recovery after TBI (Passineau et al., 2001; Gaulke et al., 2005; Sozda et al., 2010; Monaco et al., 2013). Additionally, Miller et al. (2013) have also recently

demonstrated a decrease in hippocampal volume loss in TBI patients, with increased engagement with cognitively, physically and socially demanding activities, supporting the role of EE in directly preventing neuronal death.

Post-injury EE housing has been shown to decrease injury-induced lesion volume, increase synaptic density, increase post-synaptic density (PSD) thickness, increase dendritic spine density and dendritic branching in supragranular and infragranular layers of injured cortex (Biernaskie and Corbett, 2001; Ip et al., 2002; Johansson and Belichenko, 2002; Xu et al., 2009a,b). Such structural changes may lead to EE-enabled compensation and recovery of function after injury (Rose et al., 1987; Kolb and Gibb, 1991; Whishaw et al., 1991; Passineau et al., 2001; Will et al., 2004). Under uninjured conditions, EE-induced structural changes are thought to occur due to upregulation of trophic factors such as VEGF and BDNF which promote cell survival and plasticity, and an increase in activation of transcription factors of proteins mediating plasticity (Young et al., 1999; Rampon et al., 2000; Keyvani et al., 2004; Will et al., 2004; Gaulke et al., 2005; Hoffman et al., 2008; Sozda et al., 2010; Monaco et al., 2013; Ortuzar et al., 2013). Interestingly, studies have reported an increase in BDNF expression after TBI (Hicks et al., 1997; Chen et al., 2005), with no further increase following exposure to EE (Chen et al., 2005) suggesting that EE-induced benefits for recovery after TBI may not depend on increasing the levels of trophic factors.

The effects of TBI may also be exerted through inflammatory processes: as we have noted previously (Alwis et al., 2013), activation of inflammatory cascades as part of the normal cellular response to injury can cause further injury to the already damaged brain (Menge et al., 2001; Morganti-Kossmann et al., 2002). The inflammatory response in TBI involves production of pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF-a), and anti-inflammatory cytokines such as IL-10 and IL-12, all of which are seen in the cerebrospinal fluid of TBI patients within a few hours of the primary injury. Inflammatory cytokines IL-1a, IL-1b, and IL-18 are also increased after TBI (Menge et al., 2001; Morganti-Kossmann et al., 2002). Interestingly, EE is able to decrease levels of pro-inflammatory molecules such as tumor necrosis factor alpha (TNF-α) and interleukin 1b (IL-1b; Briones et al., 2013) in the cortex and hippocampus post-injury. Given the up-regulation of these factors by TBI, the EE effect may attenuate secondary-injury related damage.

EE also induces an increase in neurotransmitter levels such as noradrenaline and dopamine, NMDA receptor expression, and brain metabolic activity, all of which are altered in TBI and have been implicated in impairment of motor and cognitive function; thus, exposure to EE could possibly regulate TBI-induced changes in these factors (Brenner et al., 1983; Boyeson and Feeney, 1990; Liljequist et al., 1993; Dietrich et al., 1994; Hamm et al., 1996).

We noted above that some work indicates that EE in animal models of epilepsy attenuates onset of seizures, a functional consequence of aberrant neuronal excitability after TBI (Pitkanen and McIntosh, 2006; Hunt et al., 2013; Shultz et al., 2013). While the exact mechanisms underlying this protective effect are unknown, it is thought to occur through an EE-induced enhancement of trophic support, changes in receptor expression and enhanced neurogenesis (as previously described; Liu et al., 1993; Cheng et al., 1995; Young et al., 1999; Reibel et al., 2000; Korbey et al., 2008).

This review shows that overall, there are insufficient data available to decide if EE effects on all of the TBI-induced molecular events noted above are all (or any of them) involved in the beneficial effects of EE in TBI. Given the limited amount of knowledge of the effects of EE specifically in TBI, it is worth also considering how EE acts therapeutically in other neurological disorders. The general trend of how EE has benefits in other brain disorders is summarized in **Table 1**, where it can be seen that EE acts to increase neurogenesis, dendritic branching and spine density, and increase the expression of growth factors (Johansson and Ohlsson, 1996; Young et al., 1999; Jadavji et al., 2006; Pereira et al., 2007; Gelfo et al., 2011; Valero et al., 2011). Similarly, recent work by Koopmans et al. (2012) has also demonstrated increased spinal cord progenitor cell differentiation and increased serotonergic innervation after experimental SCI, while others have shown increased dendritic spine density in the motor cortex (Kim et al., 2008) and increased BDNF levels (Berrocal et al., 2007). These studies, as well as those focussing on TBI, show that EE appears to be a promising post-injury treatment to improve sensorimotor and cognitive function in brain injury, most likely due to similar underlying structural and molecular mechanisms. Due to the wide and inter-connected nature of the effects of EE, it is likely that a combination of both molecular and morphological changes needs to occur in order to see improvements in neuronal function and behavior.

TIMING OF THE USE OF EE AS A THERAPY AFTER TBI

Some clues as to the potential mechanism by which EE could rescue brain function in TBI comes from the finding that the timing and duration of EE are important factors governing motor and cognitive recovery post-TBI (**Figure 2**; Hoffman et al., 2008; De Witt et al., 2011; Matter et al., 2011; Cheng et al., 2012). Thus, Hoffman et al. (2008) reported that recovery of motor and cognitive function, such as beam-walking and spatial learning and memory, depended on an optimal time and length of EE exposure relative to time after injury. After mixed focal-diffuse TBI, even a short period of EE exposure (6 h) was sufficient to improve motor and cognitive behavior to a level comparable to the enhanced performance seen after much longer (3 weeks), continuous exposure to EE (Hoffman et al., 2008; De Witt et al., 2011; Matter et al., 2011). The benefits of EE were not dose-dependent, however, as task performance in animals exposed to shorter periods of EE (2 and 4 h) did not differ significantly from those of injured animals housed in standard conditions, suggesting a minimal threshold of EE exposure is needed for beneficial effects (De Witt et al., 2011). EE-induced plasticity has persisting effects such that even limited exposure (3 weeks) to EE post-TBI can result in long-term protection from memory deficits, as assessed by the MWM task, for up to 6 months after animals are withdrawn from EE conditions (Cheng et al., 2012), making it an ideal candidate for therapy post-TBI.

Recent studies have also demonstrated that even pre-injury exposure to EE is neuroprotective (Kozlowski et al., 2004; Johnson et al., 2013). Kozlowski et al. (2004) showed that brief (15d) EE

Table 1 | Behavioral, morphological, and molecular effects of EE in various neurological disease conditions.

Neurological disorder	Behavioral effects	Morphological effects	Molecular effects	References
Stroke/hypoxia-ischemia	Improved motor function (reaching, beam-walk, rotating pole) Improved declarative memory (Novel object recognition test) Improved spatial learning and memory (Morris water maze, Radial arm maze)	Increased dendritic length and branching in cortex Preserved dendritic spine density loss/increased spine density in hippocampus, cortex Decreased cortical infarct volume Enhances cell proliferation	Increased growth factor expression	Ohlsson and Johansson, 1995; Johansson and Ohlsson, 1996; Biernaskie and Corbett, 2001; Johansson and Belichenko, 2002; Risedal et al., 2002; Dahlqvist et al., 2004; Gobbo and O'Mara, 2004; Komitova et al., 2006; Buchhold et al., 2007; Pereira et al., 2007; Rojas et al., 2013
Lesions	Improved motor function (posture, ladder climb) Improved spatial learning and memory (Morris water maze)	Increased dendritic length in cerebellum Increased dendritic branching and spine density in hippocampus, cortex	Increased growth factor expression	Kelche and Will, 1982; Held et al., 1985; Kolb and Gibb, 1991; Bindu et al., 2007; Frechette et al., 2009; De Bartolo et al., 2011; Gelfo et al., 2011
Epilepsy	Increased seizure resistance Increased exploratory activity (Open field) Improved spatial learning (Morris water maze)	Decreased hippocampal cell death Increased neurogenesis	Increased growth factor expression Enhanced expression of neuronal and synaptic plasticity mediators	Young et al., 1999; Auvergne et al., 2002; Faverjon et al., 2002; Rutten et al., 2002; Koh et al., 2007; Korbey et al., 2008
Huntington's disease	Delayed onset of motor deficits Improved spatial memory (Barnes maze, Morris water maze)	Delays degenerative loss of cerebral volume Attenuates deficits in hippocampal neurogenesis Reduced aggregation of huntingtin protein fragments	Increased growth factor expression Increased synaptic protein expression	Van Dellen et al., 2000; Hockly et al., 2002; Spires et al., 2004; Lazic et al., 2006; Nithianantharajah et al., 2008; Wood et al., 2010
Alzheimer's disease	Improved spatial learning and memory (Morris water maze, Barnes maze) Improved working memory (Radial arm water maze)	Increased/decreased Aβ and amyloid deposition Increased neuronal progenitor cell proliferation Increased/decreased neurogenesis Decreased progenitor cell survival	Increased growth factor expression Increased synaptophysin expression	Jankowsky et al., 2003, 2005; Levi et al., 2003; Arendash et al., 2004; Wen et al., 2004; Lazarov et al., 2005; Berardi et al., 2007; Cracchiolo et al., 2007; Levi and Michaelson, 2007; Valero et al., 2011
Parkinson's disease	Improved motor function (skilled reaching task)	Decreased dopaminergic neuron and transporter loss Decreased cell death	Increased growth factor expression	Bezard et al., 2003; Faherty et al., 2005; Jadavji et al., 2006

Summary of findings from studies that have investigated the effects of EE after various neurological conditions.

exposure in immature rats at p21, prior to TBI in adulthood (approximately 3 months old), results in a paradoxical increase in cortical lesion volume, but coupled with faster recovery of forelimb function, assessed by foot fault and asymmetry tests. Similarly, exposure to 15 days of EE immediately pre-TBI attenuates spatial and long-term memory deficits in the MWM task, in a manner similar to that seen after post-injury EE exposure (Johnson et al., 2013). However, the relevance of such a model in a clinical setting is limited. It is however, likely that, in accord with the Hebbian theory of plasticity, pre-injury exposure to EE acts mainly to strengthen existing connections in the uninjured brain, which may carry forward post-injury. This is likely to occur through the upregulation of trophic factors such as BDNF, which are shown to increase after exposure to motor enrichment before and after injury (Kleim et al., 2003). In contrast, post-injury EE exposure acts mainly to develop and strengthen new/previously silent/remaining connections to compensate for the damage in existing pathways (Taub et al., 2002), while elevated growth factor expression acts to limit the spread of damage (Kleim et al., 2003). This would suggest that although pre- and post-injury EE-exposure is beneficial for protection and/or recovery from injury, the underlying mechanisms may be different.

The fact that even pre-injury exposure to EE can ameliorate the effects of TBI may be taken to indicate that the benefits of EE are independent of the TBI-induced molecular and structural changes that cause deficits to brain and behavior. However, this is, as yet, an unsafe assumption for the reasons that brain processes are so highly inter-linked and often use common pathways. For example, as noted above, TBI increases inflammatory cascades while EE reduces many of the same cascades; thus

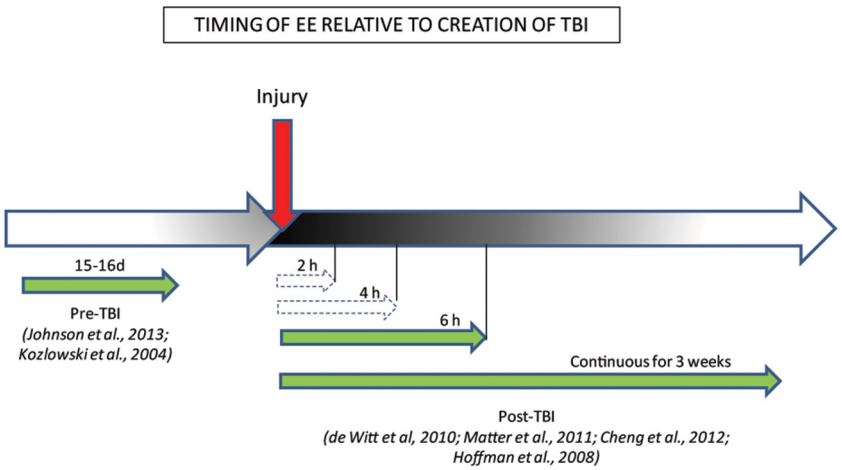

FIGURE 2 | Behavioral benefits conferred by the timing/duration of EE relative to creation of TBI. The efficacy of EE treatment when administered pre/post-injury is represented by green full-line arrows which indicate EE timing conditions that ameliorated behaviors, while white dashed arrows indicate EE timing conditions that failed to ameliorate behaviors.

down-regulation of these cascades by pre-exposure to EE may reduce subsequent TBI-induced activation of the inflammatory mechanisms and thereby reduce secondary injury processes, producing neuroprotection.

BEYOND THE BENCH

The current body of literature on the effects of EE in neurological disease indicates that EE represents significant therapeutic potential, on its own and in combination with pharmacological treatments (Kline et al., 2007, 2010, 2012), by inducing neuroprotective mechanisms involving molecular, structural, and functional processes to improve histopathologies and behavioral outcomes. Considering the many positive effects of EE demonstrated after experimental brain injury, it would be logical to try to aid recovery by applying EE in a clinical setting. Certainly, intellectually, physically and socially active lifestyles (that are akin to EE) have been linked to improved cognitive function and lower incidences of cognitive impairment, particularly in older, uninjured adults (Seeman et al., 2001; Scarmeas and Stern, 2003; Wilson et al., 2003; Newson and Kemps, 2005; Fujiwara et al., 2009; Voss et al., 2011). Similarly, cognitive enrichment early in life has also been linked to improved cognitive abilities in later life (Milgram et al., 2006), while Kramer et al. (2004) have suggested that enhanced cognitive enrichment results in improved crystallized intelligence.

Indeed, the use of EE as a rehabilitative treatment for humans post-TBI has been suggested to be effective in positively influencing long-term outcomes. However, the concept of EE for humans is more complex to define than what constitutes as EE for animals, as factors such as engagement and motivation play a role in classifying the level of enrichment an individual receives. In a clinical setting, EE can be broadly classified as a paradigm that specifically enhances and promotes engagement with cognitive, social and physical stimulation. An important caveat to the discussion about the role of EE in the treatment of TBI is that post-TBI rehabilitation programs are widely considered to be comparable to enriched environments, in that these programs often comprise of multiple components that are considered hallmarks of EE, which include physical and cognitive therapy, multi-modal stimulation, novelty, duration, functional relevance, and social integration. It has to be noted, however, that specific skill rehabilitation paradigms often do not result in improved general performance in the post-discharge environment, and instead act to improve task-specific performance (Sohlberg et al., 2000; Park and Ingles, 2001). It has instead been suggested that a more generalized treatment would be beneficial in improving overall function (Toglia, 1991; Toglia et al., 2010). Rehabilitation paradigms treating brain injury are often implemented in the acute stages post-injury, in an in-patient hospital setting. Rehabilitation based on EE principles in TBI patients results in better general functional outcomes, such as improved cognitive and motor skills (Willer et al., 1999; Powell et al., 2002; Cifu et al., 2003; Boman et al., 2004; Hayden et al., 2013), and better community integration (Zhu et al., 2001; Cicerone et al., 2004). A number of studies have also shown that increasing the duration and intensity of exposure to rehabilitative therapy results in improved recovery times (Blackerby, 1990; Spivack et al., 1992; Shiel et al., 2001; Zhu et al., 2001, 2007; Slade et al., 2002; Cifu et al., 2003; Cicerone et al., 2004).

It has also been suggested that a lack or an absence of EE is linked to cognitive decline post-injury (Till et al., 2008; Frasca et al., 2013), demonstrating the importance of continued exposure to EE in the post-discharge stages after brain injury. In that sense, a number of factors could contribute to the provision of an appropriate level of enrichment once a patient has left an intensive rehabilitative environment. These factors include ease of access to activities and resources that are cognitively, physically and socially stimulating, as well as support that encourages participation and integration with these environments (Frasca et al., 2013). Frasca et al. (2013) have also suggested that although patients eventually return to an environment that could be considered enriched post-TBI, interactions with these environments may be restricted due to limitations in cognitive

and/or physical deficits. This is especially relevant during the transition from the in-patient rehabilitation environment, to post-discharge home environments, where complexity of, and engagement with environments may reduce. A reduction in enrichment in the post-acute period could be detrimental to recovery as studies have shown that functions gained during stimulation of neural pathways (such as during rehabilitation) can be lost through under-use (Rubinov et al., 2009; Warraich and Kleim, 2010; Frasca et al., 2013). Post-discharge, the major forms of therapy mapped onto EE principles include community-based and home-based rehabilitation, with the aim that these programs would aid in improving behaviors and skills required for everyday functioning, improving community integration, and preventing cognitive decline (Fryer and Haffey, 1987; Frasca et al., 2013). Studies have shown that continued enrichment in the form of cognitive rehabilitation in the post-discharge setting (i.e., domestic or vocational environments) increases neuropsychological function, learning and memory (Willer et al., 1999; Boman et al., 2004).

Given the complexity and ethics of manipulations of the environment in humans recovering from TBI, in addition to the difficulties in accurately comparing the effectiveness of various rehabilitation paradigms, questions of the correlation between these effects and EE-induced functional changes remain. Injury heterogeneity also raises challenges in defining exactly what level of enrichment is optimal and beneficial. However, the findings presented in this section strongly suggest that EE or EE-based therapy tailored to the patient's needs could significantly improve outcomes when applied in both the in-patient, acute and post-discharge, chronic settings.

CONCLUSION

The studies described here well support the use of EE as a therapeutic paradigm in the treatment of TBI. However, while the results of these studies all show promise in improving TBI-induced histopathologies and sensorimotor and cognitive deficits, there is still much work to be done to clarify our understanding of how EE exerts its effects in disease conditions. Paramount to the understanding of how EE improves behavioral outcomes after injury is the investigation of how EE changes neuronal function post-TBI, of which we know nothing. Only once these effects are unveiled will we be able to implement EE as a treatment option post-injury at its maximum potential.

It is also worth adding the caution that while EE holds promise in its application as a therapeutic tool after brain injury in humans, the complex nature of utilizing EE in a clinical setting makes it difficult to standardize treatment and compare outcomes. It is also true that EE as an experimental paradigm in animal studies has yet to be standardized, with housing conditions, environmental stimuli, number of animals per cage, age of animals at onset of enrichment, as well as the duration of enrichment, varying markedly between studies. The extent of contribution of these factors is particularly relevant when considering the demonstrated neuroprotective effects of EE in neurological disease states, where little is known about how improved functional outcomes relate to changes in neuronal function. Using experimental models that are easily controlled and manipulated, however, would provide us with valuable insight into the therapeutic potential of EE, both in laboratory and clinical settings.

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Stem cell-paved biobridge facilitates neural repair in traumatic brain injury

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Modified mesenchymal stromal cells (MSCs) display a unique mechanism of action during the repair phase of traumatic brain injury by exhibiting the ability to build a biobridge between the neurogenic niche and the site of injury. Immunohistochemistry and laser capture assay have visualized this biobridge in the area between the neurogenic subventricular zone and the injured cortex. This biobridge expresses high levels of extracellular matrix metalloproteinases (MMPs), which are initially co-localized with a stream of transplanted MSCs, but later this region contains only few to non-detectable grafts and becomes overgrown by newly recruited host cells. We have reported that long-distance migration of host cells from the neurogenic niche to the injured brain site can be attained via these transplanted stem cell-paved biobridges, which serve as a key regenerative process for the initiation of endogenous repair mechanisms. Thus, far the two major schools of discipline in stem cell repair mechanisms support the idea of "cell replacement" and the bystander effects of "trophic factor secretion." Our novel observation of stem cell-paved biobridges as pathways for directed migration of host cells from neurogenic niche toward the injured brain site adds another mode of action underlying stem cell therapy. More in-depth investigations on graft-host interaction will likely aid translational research focused on advancing this stem cell-paved biobridge from its current place, as an equally potent repair mechanism as cell replacement and trophic factor secretion, into a new treatment strategy for traumatic brain injury and other neurological disorders.

Keywords: trauma, cell transplantation, regenerative medicine, neurogenesis, extracellular matrix

A NOVEL BRAIN REPAIR MECHANISM OF TRANSPLANTED STEM CELLS

Stem cell research offers an avenue for an in-depth study of cell biology, as well as in the development of new strategies to treat diseases (Yasuhara et al., 2006, 2008; Tajiri et al., 2012). Nevertheless, much remains to be understood about the mechanisms underlying the beneficial effects of stem cell therapy. To date, there are two major schools of discipline in stem cell-mediated repair mechanism in brain damage caused by injury or neurodegenerative disorders (Borlongan et al., 2004; Pastori et al., 2008). The first concept supports the idea of "cell replacement," i.e., stem cells implanted into the brain directly replace dead or dying cells (**Figure 1A**), whereas the other argues that transplanted stem cells secrete growth factors that indirectly rescue the injured tissue (i.e., bystander effects of stem cells) (Lee et al., 2007; Redmond et al., 2007) (**Figure 1B**).

Stem cells exist through adulthood (Ma et al., 2010), and possess the capacity for self-renewal and differentiation into multiple lineages. They have also been shown to contribute to the maintenance of homeostasis (Kim et al., 2011), exert therapeutic benefits both endogenously (Barha et al., 2011; Borlongan, 2011; Jaskelioff et al., 2011; Wang et al., 2011) and following transplantation into injured organs, e.g., the brain (Mazzocchi-Jones et al., 2009; Hargus et al., 2010; Lee et al., 2010; Andres et al., 2011; Liu et al., 2011; Mezey, 2011; Yasuda et al., 2011). There are two major stem cell niches in the brain namely, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the hippocampus dentate gyrus (DG) (Carlén et al., 2009; Sanai et al., 2011), although quiescent neural stem cells (NSCs) have been found in other brain regions (Robel et al., 2011). The discovery that stem cells are activated following injury opened up new research frontiers in regenerative medicine (Yasuhara et al., 2006; Mazzocchi-Jones et al., 2009; Hargus et al., 2010; Lee et al., 2010; Andres et al., 2011; Barha et al., 2011; Borlongan, 2011; Jaskelioff et al., 2011; Liu et al., 2011; Mezey, 2011; Wang et al., 2011; Yasuda et al., 2011; Tajiri et al., 2012). Consequently, this research paved the way for translation of laboratory studies on stem cells into limited clinical trials for brain disorders (Pollock et al., 2006; Yasuhara et al., 2009; Seol et al., 2011). Despite these scientific advances and clinical applications, the mechanisms underlying

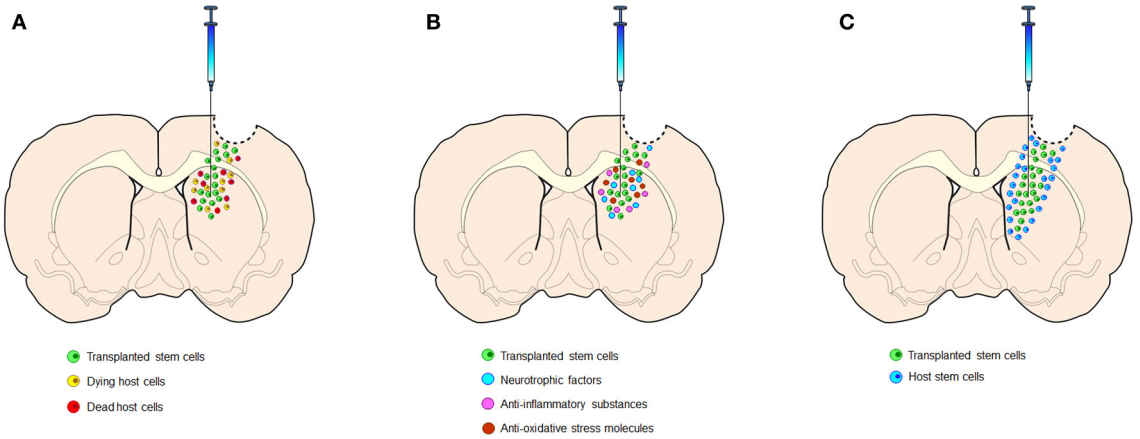

FIGURE 1 | Multiple mechanisms underlying stem cell therapy. (A) Cell replacement entails that transplanted cells replace dead or dying host cells, which would require neuronal differentiation of stem cells and reconstruction of the damaged synaptic circuitry. **(B)** By-stander effects involve secretion of neurotrophic factors, anti-inflammatory substances, and anti-oxidative stress molecules by the transplanted cells, which subsequently rescue spared host cells or stimulate neurogenesis. **(C)** Stem cell-paved biobridges show that transplanted cells form a biological pathway, enriched in MMPs, and ferries newly born host stem cells from the neurogenic niche SVZ to the injured host tissue.

stem cell-mediated repair in brain injury are not yet completely understood.

In a recent study, we demonstrated motor and neurological improvements in rats subjected to traumatic brain injury (TBI) and transplanted intracerebrally with cultured Notch-induced human bone marrow-derived mesenchymal stromal cells (referred to as SB623, supplied by SanBio Inc.) While we obtained important results that corroborate the putative therapeutic benefits of stem cell transplantation for TBI, our research on the mechanism of action of SB623 revealed breakthrough findings which support the discovery of a novel stem-cell mediated repair mechanism in brain injury. Accordingly, we observed the capacity of transplanted stem cells to harness a "biobridge" between the neurogenic niche and the site of brain injury, enabling long-distance migration of host neurogenic cells and consequently, initiating endogenous repair mechanisms. In this paper, we discuss the properties and characteristics of these stem cell paved-biobridges, elaborate on the unique mechanism by which these biobridges facilitate repair in a rat model of TBI, and importantly, suggest the clinical significance of exploiting this novel stem cell-mediated concept of brain repair for the treatment of brain injury and other neurological disorders.

BREAKTHROUGH DISCOVERY: STEM CELL-PAVED FORMATION OF "BIOBRIDGES" IN EXPERIMENTAL MODELS OF TBI

Rats subjected to TBI were intracerebrally transplanted with SB623 (gene-modified human mesenchymal stromal cells) (Zhao et al., 2007; Yasuhara et al., 2009). Thereafter, the motor and neurological functions of these rats were evaluated at 1, 2, and 3 months post-TBI, and histological studies were performed to assess the therapeutic effects of SB623 transplantation. The behavioral studies showed significant motor and neurological improvement in TBI rats which received SB623. Histological studies also showed profound reduction in TBI-induced damages to the cortical core and the peri-injured cortical areas in SB623-transplanted TBI rats. The behavioral and histological improvements, however, were achieved despite minimal graft survival—0.60 and 0.16% at 1 and 3 months, respectively. These findings led us to examine the condition of the host tissue, in view of functional recovery despite lack of graft persistence.

At 1 month post-TBI, we observed notable increases in endogenous cellular proliferation (Ki67) as well as immature neural differentiation (nestin) in the peri-injured cortical areas and SVZ, along with a stream of migrating cells along the corpus callosum (CC) of SB623 transplanted TBI animals. Furthermore, at 3 months post-TBI, we observed enhanced cellular proliferation and neural differentiation in the peri-injured cortical (CTX) areas of SB623 transplanted TBI animals, accompanied by a solid stream of neuronally-labeled cells (nestin and DCX) migrating not only along but also across the CC from the SVZ to the impacted CTX. Contrastingly, TBI rats which received vehicle infusion exhibited elevated cellular proliferation; however the newly formed cells were "trapped" within the SVZ and CTX and did not migrate to the impacted CTX.

We next analyzed the formation of the biobridge by means of the cells leaving the SVZ and moving toward the site of injury was laser captured in the animals receiving the SB623 cells.

The biobridge between the SVZ and the impacted cortex was composed of highly proliferative, neutrally committed, and migratory cells. These animals showed a 2 and 9-fold upregulation of the matrix metalloproteinase-9 (MMP) activity and expression at 1 and 3 months post-TBI, respectively. Further *in vitro* studies also showed the ability of SB623 cells to enhance cell migration via this MMP-rich signaling cues. These signals are crucial to the migration of endogenous cells which can then assist with functional recovery of damaged tissue. Merely 1 month post-TBI, a surge of proliferative Ki67 positive cells and neurally immature nestin labeled cells in the peri-injured areas and SVZ were discerned. The high level of MMP-9 in the biobridge indicates the

importance of this neurovascular proteinase. Interestingly, this proteinase was upregulated in the vehicle group, but reverted back to control-sham levels at 3 months post-TBI. This illustrates the role of MMP in long-term recovery and adds another facet to the mechanism through which stem cells aid in recovery of damaged tissue.

To provide further evidence that the implanted SB623 cells facilitated the formation of the biobridge, thus enabling the migration of host stem cells from the SVZ to the site of injury and the up-regulation of endogenous cells, an *in vitro* study was performed with primary rat cortical cells grown both alone and co-cultured with SB623 cells. These were grown either in the presence or absence of the MMP-9 inhibitor Cyclosporin-A. Migratory cell assay revealed noticeably enhanced migration of primary rat cortical cells in the chamber containing SB623, which was then significantly suppressed by treatment with the MMP-9 inhibitor. Treatment with the inhibitor alone, combined treatment with SB623 and the inhibitor, and absence of both SB623 and the inhibitor did not significantly alter migratory potential.

Although endogenous repair mechanisms are initiated post-TBI, these effects are typically limited to the neurogenic SVZ and quiescent neurogenic resident cells around the impacted cortex. Accordingly, these endogenous mechanisms are not robust enough to provide a solid defense against TBI or other disease-induced cell death cascades necessitating introduction of exogenous cells to aid migration of endogenous stem cells from the neurogenic niche to the site of injury. Stem cell transplantation into the peri-injured cortical areas purportedly creates a biobridge comprised of a neurovascular matrix which allows newly formed endogenous cells to migrate efficiently to the site of injury. Moreover, biobridge is established, exogenous cells slowly fade away, supplanted by newly formed endogenous cells that can maintain recovery even in the absence of transplanted stem cells.

A BIOBRIDGE BETWEEN THE NEUROGENIC NICHE AND THE ISCHEMIC TISSUE

The results show SB623 transplants aid in regeneration of the traumatically injured brain by constructing a biobridge between the SVZ and the peri-injured cortex (**Figure 1C**). This novel mechanism opens new doors for cell therapy by allowing the creation of similar biobridges between neurogenic and non-neurogenic sites to aid in injury-specific migration of cells across tissues that are barriers to cellular motility.

A phase I/IIa study of SB623 cell transplantation in chronic stroke patients has already been initiated. Transplantation of SB623 cells has been shown to mitigate histological and behavioral deficits associated with stroke, spinal cord injury, and Parkinson's Disease in both cell culture and animal models of brain disorders. The use of SB623 cells in TBI patients is an innovative concept that has already been FDA approved for a limited clinical trial based on the data presented.

Understanding SB623's role in facilitating the migration of endogenous cells via a biobridge exposes the active role of MMPs and ECMs in stroke pathology (Park et al., 2009; el Zoppo et al., 2012) and highlights their increasingly prominent role as therapeutic targets for stroke. Functions and levels of MMPs and ECMs have been shown to be influenced by a variety of cells coming from variable sources including umbilical cord blood, peripheral blood, and the adult brain (Barkho et al., 2008; Sobrino et al., 2012; Lin et al., 2013). This suggests a potential for these molecules to serve as biobridges similar to the current function of Notch-induced SB623 mesenchymal stromal cells.

While documented neurogenic niches such as the SVZ exist in the adult brain and contain cells that play a critical role in repairing the stroke brain (Ekdahl et al., 2009; Ducruet et al., 2012; Hassani et al., 2012; Wang et al., 2012; Trueman et al., 2013), it has been shown that a major limiting factor for endogenous repair is the lack of successful migration of newly formed host cells to the site of injury. Currently, results show SB623 cell transplantation boosts endogenous repair mechanisms by guiding the transition of new cells from the neurogenic SVZ, across a non-neurogenic brain area, to the site of injury. The ability of SB623 cells to form biobridges containing MMPs and ECMs which can then entice newly formed cells from the niche into the ischemic tissue appears to be a fundamental mechanism of action. Once the transplanted SB623 cells have pioneered the formation of these biobridges, they allow the endogenous stem cells to take over the remodeling process.

The precise mechanism by which the graft cells are integrated into the recipient brain tissue and subsequently interact with the host cells to result in functional restoration remains unknown. This essential interaction between the transplanted cell and host cell becomes even more obscure when graft survival is minimal. This indicates that the role of the SB623 is to set in motion robust and stable therapeutic benefits, particularly by leading the way for host cells to reach the injured site even across non-neurogenic and injured tissues. MMP has been implicated in chronic brain injury recovery through studies that inhibited MMPs, which consequently halted neurogenic migration from the SVZ into damaged tissues. The result was a noticeable retardation in neurovascular remodeling. This supports the concept that exogenously added cells can express MMPs and thereby reinforce the neurovascular unit, aiding in the transplant-mediated host cell migration toward the site of injury. This potentially allows for the formation of biobridges, thereby affording functional recovery in TBI.

BEYOND TBI: EXPLOITING STEM CELL-PAVED BIOBRIDGES FOR THE TREATMENT OF OTHER NEUROLOGICAL DISORDERS

The most adult stem cells in the brain are found in the SVZ of the lateral ventricles and the subgranular zone of the hippocampus dentate gyrus. The microenvironment of a stem cell niche is maintained by the signaling molecules, growth factors, and receptors. In adults, these stem cells typically remain in a dormant non-dividing state until activated by an insult. When an insult occurs motility ensues and the endogenous stem cells find themselves trapped and unable to reach the site of injury. The novel discovery that grafted cells can facilitate endogenous stem cell migration from the neurogenic niche to the site of injury is indeed a significant progress in the both stem cell and TBI research.

Our recent study (Tajiri et al., 2013) advances the concept of the biobridge mechanism as a cell mediated repair strategy in TBI, and opens new avenues for translational applications of cell therapy in TBI. Monitoring long term safety and efficacy of SB623

cell therapy in TBI animal models in order to optimize the conduct of clinical trials involving these cells in TBI patients is a priority. Gaining a more concrete understanding of the stem cell mechanism is the next step which will help to push forth the boundaries of stem cell research and explain the mechanism of cellular therapy in neurological disease.

In addition to TBI, a number of other neurological disorders are characterized by a "biological gap" between the site of injury and intact tissue. In this regard, disorders like stroke and Parkinson's disease may benefit from a deeper understanding on the concept of stem cell-paved biobridge because both disorders present with a site of cellular degeneration that is physically separated from the area of the brain that could aid in the recovery of dead tissue or lost cells. For example, stroke entails an ischemic core and penumbra residing next to intact tissue. While the ischemic core damage cannot be recovered, the potential for neural repair has been demonstrated by targeting the penumbra. Accordingly, a biobridge between the penumbra and the intact tissue (i.e., neurogenic niche) could potentially aid in stroke. Parkinson's disease involves the degeneration of the nigrostriatal dopaminergic pathway, which could improve drastically with directed migration of host stem cells toward this region in the form of a biobridge. Further investigations are warranted to determine how the concept of stem-cell paved biobridge could be exploited for the treatment of other neurological disorders.

MULTI-PRONGED MECHANISMS UNDERLYING STEM CELL THERAPY

As noted above, stem cell-mediated repair mechanisms have been widely purported as afforded via cell replacement and bystander effects (Snyder et al., 1997; Borlongan et al., 2004; Lee et al., 2007; Redmond et al., 2007; Pastori et al., 2008; Acosta et al., 2014). Our proposed third mechanism describes the recruitment of endogenous stem cells from the stem cell niches (Alvarez-Buylla et al., 2008) to the injured site through the transplanted stem cell-formed biobridge. This begs the question of whether the biobridge provides the scaffold or trophic factors to promote stem cell migration. Interestingly, new reports suggest candidate ECMs may serve as a scaffold or trophic factor-rich soluble molecules. For example, a study observed that the limits of interstitial cell migration depends upon scaffold porosity and deformation of the nucleus, with pericellular collagenolysis and mechanocoupling as modulators acting as scaffolds and assisting with biobridge formation (i.e., stem cell migration) (Wolf et al., 2013). Alternatively, a study found that functional analysis of mesenchymal stem cell proliferation, migration, and adhesion to ECMs revealed that IL-1β did not affect proliferation but served to induce the secretion of trophic factors and adhesion to ECM components such as collagen and laminin (Carrero et al., 2012).

In the end, stem cell functionality is a key factor to achieve clinically relevant outcomes of stem cell therapy. Of note, neurogenesis *per se* does not equate to these new neurons integrating with the damaged area, and that physiological and functional assays (e.g., synaptic circuitry reconstruction, evoked potentials, long-term potentiation, etc.) will be necessary to unequivocally reveal the contribution of these newly formed cells in the resulting behavioral recovery. Depending on the target disease of stem cell therapy, it is likely that neuronal differentiation to specific disease-phenotype (Hong et al., 2011), as in the case of Parkinson's disease and Huntington's disease, may be needed to produce functional effects. However, we caution that such neuronal differentiation may occur in both exogenously transplanted cells and the mobilized endogenous stem cells. Our concept of biobridge formation highlights the need for these stem cells to be guided toward the site of injury, which may facilitate the therapeutic effects of these newly formed cells that have committed to neuronally differentiated cells. Alternatively or a complement mechanism in the absence of neuronal differentiation, we also propose the biobridge-facilitated by-stander effects, in that with the directed migration of these stem cells toward the site of injury, the biobridge is able to harness the secretion of growth factors, anti-inflammatory substances, and/or anti-oxidative stress molecules close to the damaged area.

The concept of stem cell-paved biobridge may have some similarities with the use of olfactory ensheathing glia in spinal cord injury. Compelling evidence from animal models and clinical studies suggest that transplantation of olfactory ensheathing cells (OECs), specialized glia in the olfactory system, combined with specific training may be therapeutically useful in central nervous system (CNS) injuries and neurodegenerative diseases. The unique function of OECs could be attributed to both production of cell adhesion molecules and secretion of growth factors in OECs, which support neuron survival and neurite outgrowth (He et al., 2013). Another study showed that transplantation of OEG and Schwann cell (SCs) in a sub-acute phase can improve anatomical outcomes after a contusion injury to the spinal cord by increasing the number of spared/regenerated supraspinal fibers, reducing cavitation, and enhancing tissue integrity (Barbour et al., 2013). Most spinal cord injury models evaluating the therapeutic efficacy of OEC transplants have reported functional recovery via indirect and direct reparative pathways involving growth factor secretion, neuronal and axonal regeneration, and remyelination (Roet et al., 2013).

Although similarities exist between the biobridge seen with OECs in spinal cord injury and our observed biobridge in TBI, the biobridge seen in spinal cord injury involves the ensheating features of OECs, as well as the fabrication of scaffolds (such as laminin and fibronectin) and seeding the stem cells onto these matrices in order to create a biobridge. In contrast, our observed biobridge involves a natural process of the stem cells themselves serving as matrices in facilitating the migration of endogenous stem cells from the neurogenic niche toward the injured host tissue. With this in mind, a similar biobridge strategy was documented in Parkinson's disease whereby the transplanted dopamine-secreting cells were deposited along the nigrostriatal system (instead of merely transplanting the cells into the striatum) to closely reconstruct the major dopaminergic afferent and efferent pathways (Wang et al., 1996; Tang et al., 1998; Chiang et al., 2001). Compared to our observed biobridge formation, this bridging graft in Parkinson's disease is an artificial reconstruction of the dopaminergic system whereby micro-deposits of immature cells are undertaken along the nigrostriatal pathway, whereas our biobridge formation reveals a natural process of the transplanted stem cells homing from the neurogenic niche

and forming a bridge toward the injured site, and subsequently attracting endogenous stem cells to populate the biobridge and to eventually continue the brain reparative process.

Altogether, these observations suggest that while distinct mechanisms of action may be individually facilitating the neural repair of transplanted stem cells in the injured brain, overlapping regenerative processes involving cell replacement, by-stander effects, and biobridge formation may be working in tandem in realizing the therapeutic benefits of stem cell therapy.

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CASE REPORT
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Evaluating the Effect of Repetitive Transcranial Magnetic Stimulation on Disorders of Consciousness by Using TMS-EEG

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Background: The modulation efficacy of Transcranial magnetic stimulation (TMS) on consciousness improvement of patient with disorder of consciousness (DOC) has not been definitely confirmed.

Objective: This study proposes TMS-EEG to assess effects of repetitive TMS (rTMS) on brain modulation of DOC.

Methods: Twenty sessions of 10 Hz rTMS were applied over the dorsolateral prefrontal cortex for a patient with DOC. Measures of Coma Recovery Scale-Revised (CRS-R) score, TMS-evoked potential (TEP), perturbation complexity index (PCI), and global mean field power (GMFP) were used to evaluate the consciousness level of the patient at three intervals: before the rTMS protocol (T0), immediately after one session rTMS (T1), and immediately after 20 sessions (T2).

Results: It was found that the patient was diagnosed of a minimally conscious state minus (MCS-) by means of CRS-R at the interval of T0, however the TEP and PCI indicated the patient was vegetative state (VS). At the interval of T1, there was not any clinical behavioral improvement in CRS-R, but we could find significant changes in TEP, PCI, and GMFP. At the interval of T2 there was a significant increase of consciousness level according by CRS-R score, PCI value, TEP, and GMFP after 20 sessions of 10 Hz rTMS on the patient with DOC.

Conclusions: We demonstrated that TMS-EEG might be an efficient assessment tool for evaluating rTMS protocol therapeutic efficiency in DOC.

Keywords: TMS-EEG, disorder of consciousness, rTMS, perturbation complexity index, EEG

INTRODUCTION

Although, some studies have attempted to demonstrate some pharmacologic or nonpharmacologic effects, until now there were no evidence-based guidelines regarding the treatment of patients with DOC (Bernat et al., 2006). Recently, few case reports have addressed the application of rTMS on consciousness improve in patients of vegetative state (VS) or minimally consciousness state (MCS) (Lefaucheur et al., 2014). Effects of high frequency rTMS on MCS have been reported in several patients. A recent case report demonstrated that a patient in MCS has meaningful behaviors increase after received three sessions 20 Hz rTMS on the primary motor cortex (M1), it suggested that the rTMS might improve consciousness of MCS patient (Piccione et al., 2011). In a previous study (Manganotti et al., 2013), six patients in VS and MCS received one session of 20 Hz rTMS on M1 region, and one MCS patient has significant clinical and EEG modification. In a study (Naro et al., 2015), by using a protocol of 10 Hz rTMS over dorsolateral prefrontal cortex (DLPFC), three of ten patients with MCS have significant clinical improvement. Also, it was found that there was a significant improvement for VS patients after rTMS modulation. Until now, a case study was only reported that, when TMS deliver to DLPFC, a 30 sessions rTMS protocol could improve neurobehavioral change of VS patient (Louise-Bender Pape et al., 2009). Basically, rTMS modulation for DOC patient might be available.

How to evaluate the modulation of rTMS on the DOC patient is a critical issue. The current gold standard for assessing consciousness state is based on the standard behavioral assessment (Monti and Sannita, 2016). However, possible confounding factors and mechanisms underlying impaired brain function may not be fully considered. The absence of behavioral evidence of command following was not necessarily indicative of the true absence of consciousness (Owen et al., 2006). It was reported that the behavioral abilities could fluctuate across time which would cause mis-diagnostic (Monti and Sannita, 2016). Recently, several "stimulate-response" methods, such as short-latency evoked potentials (Cavinato et al., 2009; Ragazzoni et al., 2013), event-related potentials (Kotchoubey et al., 2005; Rohaut et al., 2015), and motor evoked amplitude (Naro et al., 2015) have been used as more objective assessment methods for the consciousness level of patient with DOC. However, the proposed methods did not consider the integrity of sensory or peripheral nerve pathways of DOC. Thus, it is necessary to develop a new and reliable method to accurately assess the clinical variety in DOC treatment.

Recently TMS-EEG was proposed to evaluate the consciousness state in severely brain-injured and disable of communication patients (Rosanova et al., 2012), and it could invariably trigger complex activations that sequentially involved distant cortical areas ipsi- and contralateral to the site of stimulation in MCS which was different from VS. TMS-EEG technique could directly detect the relationship between non-invasive stimulation and cortical response, and it should not depend on the condition of participant.

Although, TMS-EEG has been demonstrated helpful in differentiating MCS from VS, there were rarely studies using this technology to assess the efficiency of present therapy in DOC. The primary aim of this study was to explore TMS-EEG evidence in consciousness recovery during a therapy of rTMS protocol. The second aim was to support an example of using TMS-EEG to assess the therapy efficiency in DOC.

BACKGROUND

The patient is a woman age 47 with brain injury induced by hypertensive cerebral hemorrhage of right basal ganglia region. Post-injury, the patient remained behaviorally unresponsive for a period of 2 months based on available records and appeared unstable source location of pain after 8 weeks of injury. At about 10 weeks post-injury, the patient was transferred to a comprehensive inpatient brain injury rehabilitation program where physical, occupational, speech, and related therapies were performed for the next 7 months. But no distinct behaviorally improvement during this period. It was 9 months after-injury when she began to accept rTMS therapy, she was diagnosed as MCS- by CRS-R. She could open her eyes spontaneously, and blink when received big sound stimulation like clap but can't locate the sound source, noxious stimulation withdrawing the respective limb from the pain source. She can't sound and had no any commands following response, her mouth had reflex movement. Her caregivers reports that, she had relative stable sleeping time in afternoon and after midnight.

MATERIALS AND METHODS

Subjects

Written informed consent to participate in the study was obtained from the patient's caregivers. In order to indicate the difference of TMS-evoked potential (TEP) between the patient with DOC and controls, five age matched female healthy subjects age 43–50 participated to this study to obtain the mean control TEP. Written informed consent to subjects in the study was obtained. The present study was approved by ethics committee of Beijing Army General Hospital.

Stimulation Protocol

The process of the intervention and evaluation could be found in **Figure 1**. The patient received active 10 Hz rTMS over left DLPFC. Different from similar study (Naro et al., 2015), our protocol lasted 20 consecutive days. Daily sessions of intervention consisted of 1000 pulses (10 Hz) at an intensity of 90% RMT. The stimulation of one session included 10 trains, each train lasted 10 s with a 60 s inter-train pause. The rise time of the magnetic monophasic stimulus was about 100 μs and time to zero was about 800 μs. TMS pulses were delivered using a Magstim R^2 stimulator with a 70 mm figure-of-eight coil (Magstim Company Limited, Whitland, UK). Stimulation intensity varied across this experiment was determined relative to the resting motor threshold (RMT), defined as the lowest TMS intensity which could evoke at least 5 out of 10 EMG with an amplitude >50 μV peak-to-peak in the relaxed first dorsal interosseous muscle of the right hand. To avoid

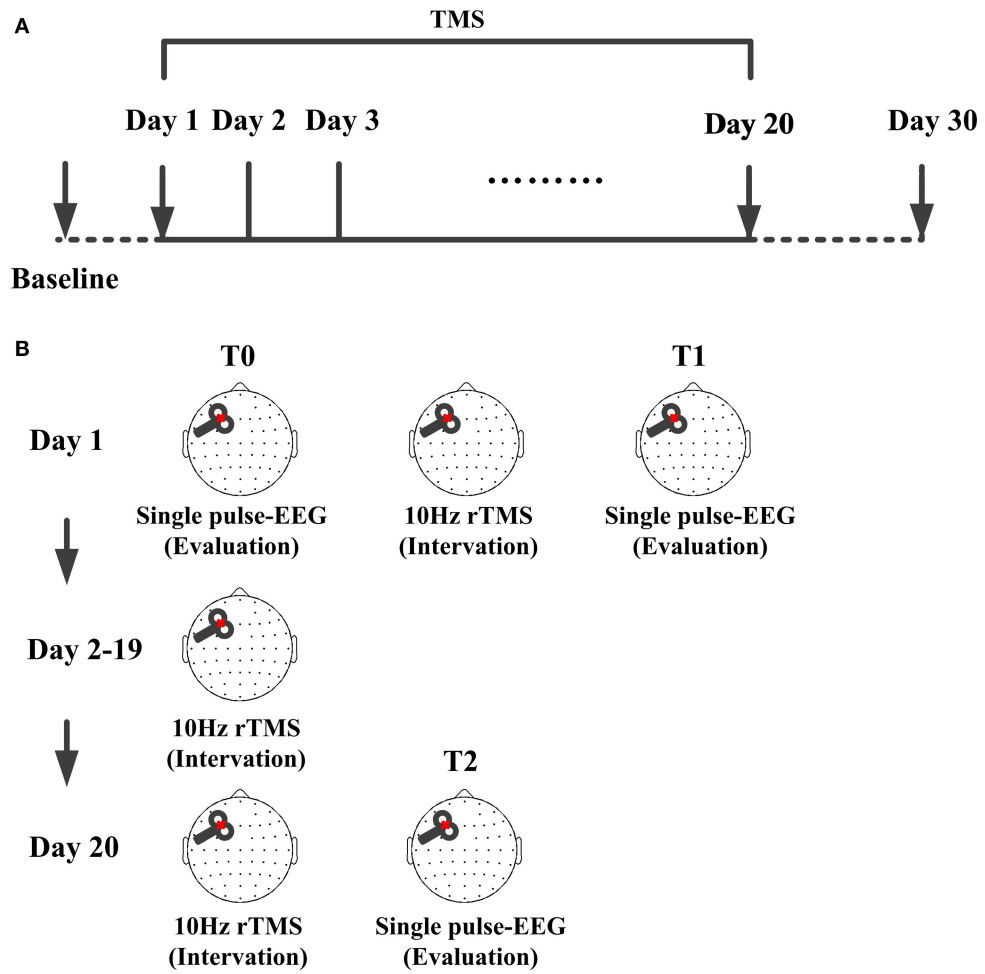

FIGURE 1 | TMS protocol for the patient. (A) Time points of the protocol, TMS were delivered at left-DLPFC lasting for 20 consecutive days. CRS-R score was assessed each day from the baseline to day 30. **(B)** Single pulse TMS evoked EEG recording before the protocol were used as baseline (T0) and that immediately after one session were used as the one session assessment (T1). From day 2 to day 19, there were no TMS and EEG evaluation. Single pulse TMS evoked EEG recorded immediately after the 20 sessions were used as assessment of the whole protocol (T2).

contamination of TMS-evoked potential by auditory potentials evoked by the click associated with the TMS discharge, patient was wearing inserted earplugs continuously playing a masking noise.

CSR-R

The CRS-R is a tool to characterize the level of consciousness and to monitor neuro-behavioral recovery in patients with DOC (Giacino et al., 2004). Scoring is based on the presence or absence of specific behavioral responses to sensory stimuli administered in a standardized manner, with low item represents reflexive activity and high items represent cognitively mediated behaviors. In this study, CRS-R was assessed daily from 1 day before rTMS protocol to30 days after this protocol.

TMS-EEG Recordings

In the experiment, we used TMS-compatible EEG recorder (BrainAmp 64 MRplus, BrainProducts), EEG was continuously acquired from 62 channels with positions of the international 10–10 system. The equipment used TMS-compatible sintered Ag/AgCl-pin electrodes. We set a band-pass filtered at DC to 1000 Hz in the recorder, and the EEG signal was digitized at a sampling rate of 2.5 kHz. During the experiment, the skin/electrode impedance was maintained below 5 kΩ. EEG was recorded in day 1 and day 20. As shown in **Figure 1B**, at T0, 200 single pulses were delivered before the protocol as baseline assessment and TMS evoked EEG immediately recorded after 10 Hz rTMS to evaluate the efficacy of one session rTMS. At T2, 200 single pulses were delivered immediately after rTMS to assess the performance of whole protocol. EEG recordings were carried out while patients were behaviorally awake (eyes open, EO) during the modulation and assessment. If the patient showed signs of sleepiness (prolonged eye closure, EC), the CRS-R arousal facilitation protocol was applied, or the experiment was suspended.

EEG Analysis

Evoked Potential by TMS

Off-line analysis was performed with EEGLAB 12.0.2.5b, running in a MATLAB environment (Version 2013b, MathWorks Inc., Natick, USA). The continuous EEG signal was segmented into epochs starting the TMS pulse onset and ending 300 ms (Massimini et al., 2005; Ferrarelli et al., 2010; Ferreri et al., 2011) after it. After this, data 20 ms after TMS pulse were removed from each trial to exclude the TMS artifact through the cubic interpolation function of MATLAB (Thut et al., 2011). Independent component analysis (ICA) function was used to identify the TMS unrelated artifacts (such as eye movement and muscle artifacts). Then each component was visually inspected in terms of scalp distribution, frequency, timing, and amplitude. The components deemed as artifact were removed with ICA (Casula et al., 2014). The 50 Hz artifact was removed from remaining trials using a notch filter. Then, EEG data were average referenced; down-sampled to 500 Hz, band pass filtered (1–80 Hz), and baseline corrected over 300 ms pre-stimulus. Single trails were carefully inspected to ensure absence of residual TMS artifacts. Each TMS-evoked response was obtained by averaging 150–200 artifact-free trials.

Perturbation Complexity Index

An index of consciousness, called the perturbation complexity index (PCI), was applied to evaluate the consciousness level of the patient. The PCI was proposed before (Casali et al., 2013), the calculation mainly includes three steps. Firstly, TMS evoked cortical perturbation (300 ms after TMS pulse) which was recorded by high-density EEG (62 channels in this study). Then source modeling was performed and nonparametric statistics extracted a binary matrix $[SS(x, t)]$ which describes the spatiotemporal pattern of activation caused by the TMS perturbation. At last, the Lempel-Ziv complexity index was used to compress the matrix. The PCI index was calculated as the normalized Lempel-Ziv complexity. The PCI is expected to be low if there is reduced interaction among cortical areas and will be high if interaction of the cortical areas increased. As suggested (Casali et al., 2013), the PCI values in VS were range of 0.19–0.31 and in MCS were range of 0.32–0.49.

Global Mean Field Power

In order to obtain the overall amount of electrical activity induced by TMS, the global mean field power (GMFP) was calculated with the multichannel average signals as follows (Lehmann and Skrandies, 1980):

$$\mathrm{GMFP\ (t)} = \sqrt{\frac{\sum_i^k (V_i\,(t) - V_{mean}(t))^2}{k}} \qquad (1)$$

where k means the number of channels, V_i means the amplitude of channel I, and V_{mean} is the mean value of the amplitude across all channels.

RESULTS

CRS-R

CRS-R were used to assess the consciousness level of the patient (**Table 1**). CRS-R score of 8 was marked at baseline. With the rTMS protocol starting, the score remained unchanged for the first 8 days. Although the patient care claimed that the patient showed more excitation, more sensitive to stimulation and less sleeping time, there were no significant clinical behavioral improvement expressed in CRS-R. In the day 9, some simple finger movements were found, and the CRS-R score increased to 10. From the day 15 to 20, the patient represented stable simply movement following the command with score of 13, and her eyes could track movement of objects like mobile phone with video. In the last week of this protocol, there was one score increased for her concentration on something for a time. The shadow area in the **Table 1** shows the CRS-R values in 20 days with 10 Hz rTMS. In the shadow area, the consciousness level of the patient arose from MCS− to MCS+ with score from 8 to 13.

TMS-EEG

TEP

Single pulse evoked potential over DLPFC was calculated at T0, T1, and T2, could be seen in **Figure 2A**. Black line shows the TEP over DLPFC calculating of mean of healthy subjects. We could see that the TEP of T0 shows simple positive-negative EEG response with positive peak at about 35 ms and negative peak at about 60 ms. The TEP of the T1 shows more channels' response activity than T0 while the TEP of the T2 shows more complex than the T1 with bigger amplitude of the fluctuation. Comparing with the TEP of the healthy subjects, the TEP of T2 appears similar fluctuation: positive peak at about 180 ms, which never occurred before.

Figures 2B–D show the butterfly plots of the TEP at three time point, respectively. There have nearly same temporal distribution of the peaks for T0 and T1, but very different from T2. Then PCI was calculated for quantifying the TEP. The first row under the butterfly plot shows the source modeling of corresponding TEP peaks. And then nonparametric statistics was performed to obtain a significant activation distribution (last row of each figure), where the black regions in the cortical represent significant cortical activation induced by the stimulation. The

TABLE 1 | Data of the CRS-R score in this protocol.

Time	CRS-R							CS
(day)	Auditory	Visual	Motor	Oro-motor	Comm	Arousal	Total	
Baseline	1	1	3	1	0	2	8	MCS−
1–8	1	1	3	1	0	2	8	MCS−
9–14	3	1	3	1	0	2	10	MCS+
15–20	4	3	3	1	0	2	13	MCS+
20–22	4	3	3	1	0	2	13	MCS+
23–30	4	3	3	1	0	3	14	MCS+

Shadow area shows the score during rTMS sessions. Comm, communication; CS, consciousness state.

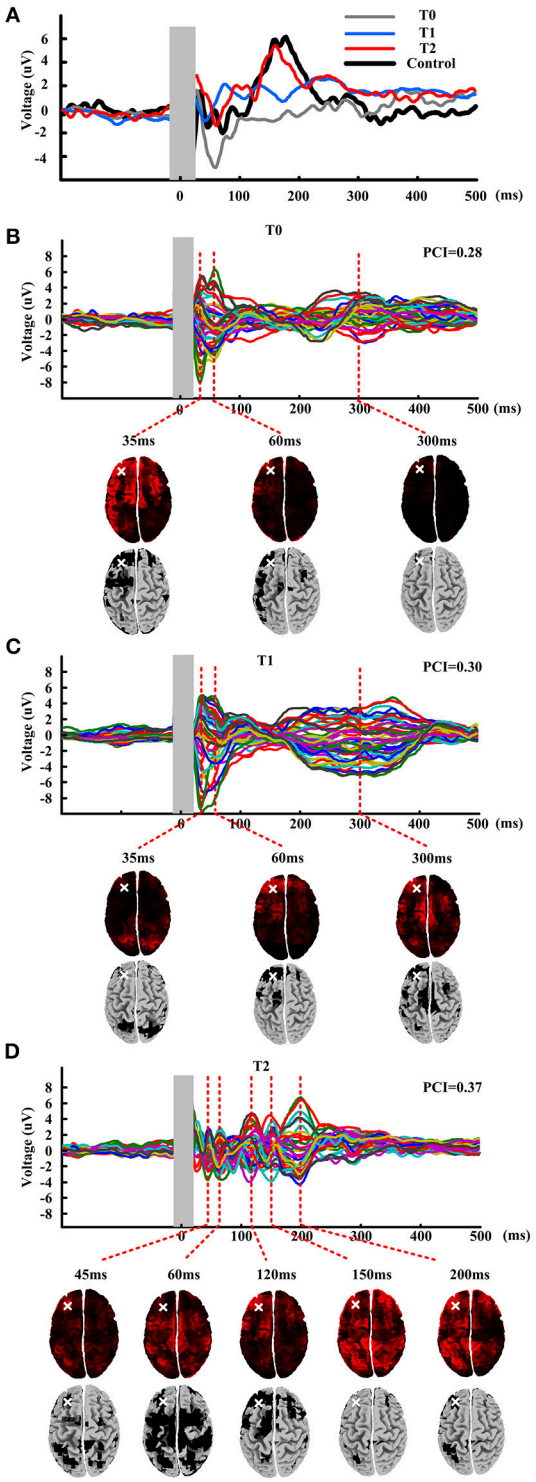

FIGURE 2 | TMS evoked potential and butterfly plots at three time points: T0, T1, and T2. (A) TMS evoked potentials of mean of healthy subjects and patient at three time points. Shadow area means 10 ms before to 20 ms after the TMS onset. **(B–D)** Butterfly plots of patient at three time points. Source modeling corresponding to each TEP peaks is given under the butterfly plots. Last row of each figure gives the significant activation distribution. White cross shows the stimulation site.

activation distribution of T0-T1-T2 indicate a trend of from local to global and from ipsilateral to contralateral. After compressing the binary matrix, the PCI was obtained. At T0, the PCI value was 0.28 and after one session rTMS, the PCI value raised to 0.30. After all the protocol, the PCI value raised to 0.37.

GMFP

The GMFP is depicted in **Figure 3**. The black line shows the mean GMFP of the healthy subjects and the red lines show the GMFP of the patient at three different time. The correlation coefficient (Matlab code: corrcoef.m) were calculated of the GMFP after stimulation between the patient and the healthy subjects. At T0, the correlation is 0.2 and T1 the correlation arose to 0.22. Different from the mean value of healthy subjects, the activation power of the global brain for the T0 and T1 mainly distributed within 100 ms after stimulation. And during the time window from 250 to 400 ms, the global brain power were activated at T0 and T1 while the healthy subject didn't show any activation. After all the rTMS protocol, the GMFP pattern of the patient was similar with the mean GMFP of healthy subjects with correlation 0.86. Meanwhile, the time window of main activation power of the patient was well-matched with the healthy subjects, and main power occurred within 300 ms after stimulation.

DISCUSSION

TEP

Measuring the EEG responses to TMS to differentiate different consciousness states had been proposed (Rosanova et al., 2012). Similar with that observed in unconscious sleeping or anesthetized subjects (Massimini et al., 2005; Ferrarelli et al., 2010), in awake VS patients, TMS triggered a simple, local slow response that indicated a breakdown in effective connectivity. While TMS triggered complex activations that sequentially involved distant cortical areas ipsilateral and contralateral stimulation site in MCS patients. The baseline TEP of the patient in this study showed a relative simple and slow curve similar with VS introduced by Rosanova et al. (2012). It did exactly matched the clinical behavioral result which was diagnosed as MCS- with CRS-R score of 8. The possible reason is due to the fluctuations in behavioral abilities across time. After one session rTMS, TMS triggered more channels' activity. After all the rTMS protocol, the TEP represented a more complex curve, which combined with the theory linking integration and differentiation to consciousness indicated a positive modulation effects of rTMS on this patient.

PCI

The PCI is a measurement to quantify the complexity of TEP and it measures the amount of information integration and differentiation within the brain's response to perturbation. The PCI value of the patient in this study arose from 0.28 to 0.37. As described by Casali et al. (2013) the PCI ranged from 0.19 to 0.31 for a stable clinical diagnosis of VS, and ranged from 0.32 to 0.49 for MCS patients. Therefore, according to the PCI values, the patient was diagnosed as a VS before rolling in this TMS

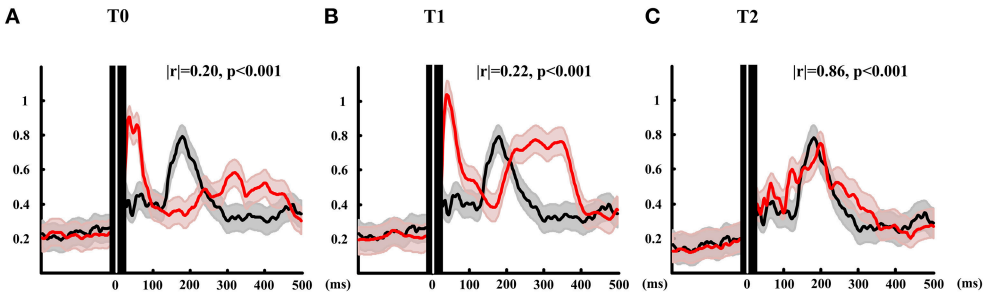

FIGURE 3 | GMFP calculated of patient at three time points and the mean of healthy subjects. Red lines show the GMFP curves of the patient at T0 **(A)**, T1 **(B)**, and T2 **(C)**. Black lines show the mean GMFP curves of healthy subjects. The gray and red shadow means standard deviation of patient and healthy subjects, respectively. Black area with white line show 10 ms before and 20 ms after TMS onset.

protocol, and it was still staying in VS after one rTMS session despite an increase of PCI value. After all the protocol rTMS, the PCI indicated that the patient was staying in MCS+. The TEP results and CRS-R score were consistent with the variation tendency of PCI and both indexes indicated an improvement of consciousness state. But the PCI values showed VS state of the patient at baseline which was not agreement with the CRS-R score. Consistent with the TEP results, the PCI values also showed that patient was still in vegetate state, although appeared much fast oscillation in TEP after one session rTMS, it indicated the patient didn't emerge from vegetate state. Indeed, the boundary of PCI used to differentiate VS from MCS was not perfectly accurate as the study just enrolled few patients for calculating, six for VS and six for MCS. But the PCI values might be useful as a significant potential diagnostic tool for consciousness evaluation.

GMFP

The GMFP results of this study showed that, at a global level, one session rTMS over the left DLPFC increased cortical excitability in temporal windows of 30–100 and 200–400 ms after stimulation. Interestingly, when comparing with healthy subjects, there was a global activation after 300 ms of stimulation for baseline and one session TEP, which nearly impossibly occurred in healthy subjects even in consciousness reduced states such as anesthesia (Ferrarelli et al., 2010) and sleep state (Massimini et al., 2005). The possible reason is that the "overtime" activation may be induced by abnormally electrical transmission evoked by damaged brain region. Then after 20 sessions rTMS, the brain activation pattern (amplitude and time) was tend to well-matched with the healthy brain. Hence, combined with the clinical behavioral assessment in CRS-R scores, we suggested that GMFP might be also a significant marker for consciousness recovery of DOC.

Overall, although there had some diversity in evaluating the base line and one session, all the assessment methods proposed in this case study consistently indicated that the consciousness state was improved after all the rTMS protocol. This divergence of the baseline assessment might be induced by fluctuation of state of the patient and the sensitivity of assessment method should be tested in quantity application. On the other hand, as demonstrated in Naro et al. (2015), we suggest that one session rTMS indeed has transiently improvement but it may difficult leading to permanent clinical behavioral change. Thereby, in this study, we used 20 sessions to use the accumulation efficacy of the rTMS modulation. The incubation time was 8 days in this study but 10 days was reported in a patient in Louise-Bender Pape et al. (2009), we think that this modification efficiency may be variable in individual level and depend on the time and intensity of rTMS.

CONCLUDING REMARKS

This was first study on reporting TMS-EEG based characteristic of consciousness recovery during rTMS protocol. The results indicated that the TMS-EEG might lead to more objectively evaluation of consciousness and might be an efficient assessment tool for rTMS protocol therapeutic efficiency evaluation. Our study was an example of using TMS-EEG method to assess an therapy efficiency in DOC. And we suggest that methods of TMS-EEG supported in this study may facilitate therapy improvement in DOC.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication. YB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design, acquisition, analysis, or interpretation of data: YB and XX. Administrative, technical, or material support: XX, JK, XY, and YY. Study supervision and obtained funding: JH and XL.

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Non-invasive brain stimulation for the treatment of brain diseases in childhood and adolescence: state of the art, current limits and future challenges

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In the last decades interest in application of non-invasive brain stimulation for enhancing neural functions is growing continuously. However, the use of such techniques in pediatric populations remains rather limited and mainly confined to the treatment of severe neurological and psychiatric diseases. In this article we provide a complete review of non-invasive brain stimulation studies conducted in pediatric populations. We also provide a brief discussion about the current limitations and future directions in a field of research still very young and full of issues to be explored.

Keywords: pediatric brain stimulation, vascular diseases, epilepsy, ADHD, Tourette, autism, depression, schizophrenia

INTRODUCTION

In the last decades the interest in exploring therapeutic and/or rehabilitative effects generated by non-invasive brain stimulation techniques in neuropsychiatric diseases increased considerably. Although this field of research encompasses numerous stimulation techniques, neuroscientists have primarily focused investigations on the use of two techniques, namely Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS). In healthy adults, these non-invasive brain stimulation techniques are applied to monitor cortical excitability/dynamics (e.g., single pulse TMS, double pulse TMS), and as neuromodulatory techniques [e.g., repetitive TMS (rTMS), tDCS]. Whereas TMS is primarily used to investigate brain physiology (e.g., task-dependent alterations of cortical maps, excitability, and so on, in health, and disease), the latter techniques are applied to *modify* physiology, and performance. Accordingly, these methods have been adopted to explore, and modulate brain functions such as language (e.g., *rTMS*: Flöel et al., 2008; *tDCS*: Vicario and Rumiati, 2012;), learning, and long-term memory formation [e.g., single pulse *TMS* (spTMS): Vicario et al., 2013a; *tDCS*: Nitsche et al., 2003], working memory (WM) (e.g., *TMS*: Gaudeau-Bosma et al., 2013; *tDCS*: Fregni et al., 2005a) perception (e.g., *TMS*: Hamilton et al., 2013; *tDCS*: Vicario et al., 2013b), and attention (e.g., *TMS*: Lee et al., 2013; *tDCS*: Tanoue et al., 2013), in healthy humans (see Nitsche et al., 2003, 2008; Kuo and Nitsche, 2012 for further examples and Nitsche and Paulus, 2011 for a complete review).

Non-invasive brain stimulation is applied also to rehabilitate cortical functions in neuropsychiatric diseases via induction of neuroplasticity. rTMS has been shown to improve cognitive functions in Parkinson's disease (Pascual-Leone et al., 1994), and improved aphasia (Naeser et al., 2005), motor control after stroke (Takeuchi et al., 2005), epilepsy (see Nitsche and Paulus, 2009 for a review), and depression (Pascual-Leone et al., 1996; O'Reardon et al., 2007), amongst others (Kammer and Spitzer, 2012).

Encouraging clinical effects have been documented also for tDCS, so far in pilot studies. tDCS improves motor and non-motor stroke symptoms (e.g., Fregni et al., 2005b), depression, and might have effects on craving, schizophrenia, and dementia, amongst others (for comprehensive reviews, see, Flöel, 2013; Krause et al., 2013; Kuo et al., 2013). All these results encourage the future therapeutic application of non-invasive brain stimulation techniques also in pediatric populations affected by brain disorders. However, the number of non-invasive brain stimulation studies conducted in childhood is scanty, especially if compared to that available from adult participants.

Two previous reviews (Quintana, 2005; Croarkin et al., 2011) gave an overview of the application of rTMS in children and adolescents. Here, we provide the reader with an updated state of the art of application of non-invasive brain stimulation in general (rTMS and tDCS) in pediatric populations. Moreover, we will discuss current limits and possible future applications of these techniques for the treatment of brain dysfunctions affecting childhood. It is beyond the scope of this review to discuss the mechanisms of how TMS and tDCS alter neural activity and induce brain plasticity in detail. For obtaining this information, some recently published articles provide a complete and exhaustive overview (see for example Stagg and Nitsche, 2011; Freitas et al., 2013; Krause et al., 2013).

NON-INVASIVE BRAIN STIMULATION FOR ENHANCING BRAIN DISORDERS IN CHILDHOOD

VASCULAR DISEASES

Pathophysiologically, stroke is associated with hemispheric dysbalance, i.e., a reduction of the activity of the lesioned brain area and an enhanced activity of the contra-lesional homologous region, which limits re-gain of functions (see Grefkes and Fink, 2011 for a recent review).

Kirton et al. (2008) conducted the first randomized sham-controlled rTMS trial in children (median age 13.25) affected by arterial ischemic stroke. Patients were affected by unilateral hand motor weakness. They received 8 days to 1 Hz rTMS of the contralesional motor cortex, which inhibits regional brain activity (Pascual-Leone et al., 2005) and increases contralateral cortical excitability via reduction of interhemispheric inhibition (Pal et al., 2005). Grip strength increased after real rTMS only, and this effect persisted until day 17 after the start of treatment. Furthermore, rTMS was well tolerated with no relevant side effects.

Valle and colleagues (2007) applied a 5-day course of rTMS upon the affected motor cortex in seventeen children (mean age 9) affected by infantile cerebral palsy and spastic quadriplegia. The study was designed according to the hypothesis that an increase of motor cortex activity would increase its inhibitory influence on spinal excitability, and thus improve spasticity. Patients received five consecutive sessions of rTMS in a randomized, sham controlled, double-blind, parallel, clinical trial design. According to previous works (e.g., Quartarone et al., 2005) showing that 5 Hz rTMS of the primary motor cortex induces an overall increase of excitability of the corticospinal output system, including spinal motoneurons, the authors report a significant reduction of spasticity only in association to this stimulation protocol. Both studies show a potential of rTMS for rehabilitation of motor symptoms originating from vascular injuries in childhood. However, due to the limited number of studies, we are still far from achieving a clear picture of the use of this technique to treat vascular problems in children. No studies for the treatment of vascular disorders in children or adolescents have been conducted with tDCS so far.

EPILEPSY

The pathophysiological substrate of epilepsies and the proneness to develop seizures is an enhanced cortical excitability, leading to paroxysmal depolarization shifts, an enhanced probability of high-frequent and hyper-synchronous activity of neuronal networks (Stafstrom, 2006; Dudek and Sutula, 2007). A reduction of neuronal excitability is the common aim of antiepileptic therapies.

Fregni et al. (2005c), tested the effect of a single 0.5 Hz rTMS session in an open study. Three pediatric patients with focal epilepsy were included. The TMS coil was positioned over the epileptogenic region, or, if this could not be clearly identified, over Cz. rTMS significantly reduced the frequency of epileptiform discharges (ED) for up to 15 and 30 days after rTMS treatment.

The study of Brasil-Neto et al. (2004) included a 6 years old patient. This patient was affected by left fronto-central slow activity. 0.3 Hz rTMS was applied once per day for 3 months. In this case, rTMS treatment was ineffective. Graff-Guerrero et al. (2004) conducted one session of 20 Hz rTMS in two patients (7 and 11 years old) suffering from epilepsia partialis continua (EPC). The patients were first submitted to a single photon emission computed tomography (SPECT) session in order to localize the focal frontal hyperperfused region to define the stimulation site; after rTMS, patients were SPECT-monitored again in order to identify perfusion alterations of the stimulated region. Indeed, cortical perfusion of the stimulated area was reduced in both patients. However, only in one patient epileptic seizures decreased significantly. Morales et al. (2005) conducted a case study involving 2 patients (8 and 16 years old) affected by EPC. One Hertz/six Hertz rTMS were applied in different sessions. No adverse effects occurred, but the treatment resulted in no clinical effects. Kinoshita et al. (2005) treated a 16 years old male suffering from parietal lobe epilepsy with 0.9 Hz rTMS over 5 days. The coil was placed over PCz. No significant improvements have been documented for this patient.

San-Juan et al. (2011) applied cathodal tDCS over the F2 scalp site in a 17 years old patient affected by Rasmussen's encephalitis [4 tDCS sessions of 60 min (on days 0, 7, 30, and 60)]. At follow-up evaluations 6 and 12 months later, seizure frequency was significantly reduced. Additionally, the patient had improved levels of alertness and language. No side effects have been reported. Yook et al. (2011) applied cathodal tDCS applied upon the epileptogenic focus in a 11 year's old patient. The patient was diagnosed with congenital bilateral perisylvian syndrome. Cathodal tDCS was applied over the right temporo-parietal area that showed epileptiform activity in the EEG for 2 weeks. During the two-month period after treatment termination, only six seizures occurred (compared to eight seizures a month before the treatment), and seizure duration decreased. tDCS was repeated for another 2 weeks, 2 months after the first intervention session. For the following two months, only one seizure occurred. No notable side effects of stimulation were observed.

In contrast, in a group of pediatric patients (age range 6–11) showing continuous spikes and slow waves during sleep (CSWS), one session of cathodal tDCS over the peak negativity of the epileptogenic pattern revealed an effect on EEG patterns only in 3 patients (Varga et al., 2011). One reason for this negative result might be that the multifocal/diffuse and poorly defined origin of epileptic activity in CSWS makes it difficult to identify the optimal region for stimulation (Brazzo et al., 2012). Moreover, stimulation was performed with 1 mA in only one session in the latter study, which might have not been sufficient to obtain significant or lasting effects.

More recently, Auvichayapat et al. (2013) enrolled thirty six children (age range 6–15 years) with focal epilepsy in a crossover sham-controlled study. Participants received a single session of cathodal tDCS upon the epileptogenic region. Active tDCS treatment was associated with significant reductions in epileptic discharge frequency immediately and 24 and 48 h after tDCS. Moreover, 4 weeks after treatment, a small (clinically negligible but statistically significant) decrease in seizure frequency was detected. All patients tolerated tDCS well.

These studies deliver some preliminary hints for a possible efficacy of rTMS, and tDCS, to treat epilepsy in children. However, the heterogeneity of the results, possibly due to different stimulation parameters, small numbers, and different etiologies of participants, and the heterogeneous quality of the studies, do not allow to draw definite conclusions.

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent and impairing disorder, characterized by inattention, hyperactivity, and executive dysfunction. Functional neuroimaging studies have shown functional and abnormalities in cingulate, frontal and parietal cortical regions, including hypoactivation (Bush, 2011). Thus, non-invasive brain stimulation procedures to improve ADHD symptoms are oriented toward excitatory protocols.

Weaver et al. (2008) performed a randomized, sham-controlled, crossover study involving 9 participants affected by ADHD. The age range of the 4 included adolescents was between 15 and 17 years. 10 Hz rTMS over 2 weeks was applied upon the right DLPFC. Clinical global impression and the ADHD-IV scales improved significantly, but similarly for active and sham rTMS. No serious adverse effects did take place. No studies on childhood ADHD have been performed with tDCS so far.

TOURETTE SYNDROME

Tourette's syndrome (TS) is one of the most common neurobehavioral disorders in childhood (see American Academy of Pediatrics, 2000). The pathology is characterized by the presence of tics, which are rapid, stereotyped movements and vocalizations, virtually involving all body segments (Vicario et al., 2010). The neuro-functional profile of childhood TS is characterized by impairment of neural circuits linking the cerebral cortex to the striatum and other sub-cortical regions (Swain et al., 2007; Bush, 2011).

Of interest for the current discussion is the Supplemental Motor Area (SMA). The pre-motor cortex has been reported to be hyperexcitable in patients with TS (George et al., 2001). Therefore, excitability-reducing rTMS to the SMA may be an effective way to treat TS, because this region is extensively connected with regions implicated in motor control (Picard and Strick, 2001).

In an open label 12 weeks cohort pilot study (Kwon et al., 2011), 1Hz rTMS was applied over the SMA for 10 days. At the end of each day subjects completed objective ratings of ADHD, mood, anxiety, tics, and side effects. Statistically significant reductions were seen in the Yale Global TS Severity Scale over the 12 weeks of the study. Le et al. (2013) tested the effect of 1 Hz rTMS upon the SMA in 25 children with TS (aged less than 16 years) for 20 days. Results document a significant improvement of clinical symptoms. Interestingly, the benefits lasted for up to 6 months in 68% of subjects. No studies for TS treatment have been conducted with tDCS. The results provided in these two studies are coherent in terms of therapeutic benefits, stimulation site (SMA) and rTMS frequency (1 Hz). However, an important limit of these studies is the lack of a control group.

AUTISM SPECTRUM DISORDER (ASD)

This syndrome is characterized by a marked decrease in social integration and communication, and affects ∼1 in 150 children (Fombonne, 2009). Increased gamma-band responses to several cognitive processes in children with autism spectrum disorder have been described (McFadden et al., 2012). While its precise role is unclear, it is implied in a wide range of processes such as attention (Lakatos et al., 2008), WM (Tallon-Baudry et al., 1998), and language (Tavabi et al., 2011). Non-invasive brain stimulation has been adopted for modulating this physiological parameter and therefore improve the related cognitive abilities.

Baruth et al. (2010) report clinical improvements in pediatric ASD induced via rTMS ($\leq$1 Hz) in a controlled study, the electrophysiological effects of 12 low frequency rTMS sessions, bilaterally applied to the DLPFC were explored in 25 subjects (ages range 9–26) with ASD and 20 age-matched controls. rTMS was administered once per week. The first six treatments were performed over the left, and the remaining six over the right DLPFC. Patients showed significant improvement in discriminatory gamma activity and also significant improvements in behavioral parameters. In another study (Sokhadze et al., 2010) 20 subjects (age range 10–19) with ASD received the same protocol. Performance was tested with the oddball paradigm, which explores attentional shifting (García-Larrea et al., 1992). rTMS minimized early cortical responses to irrelevant stimuli, increased responses to relevant stimuli, reduced the error percentage and repetitive-ritualistic behavior.

Schneider and Hopp (2011) conducted an open tDCS study in children with autism. The purpose was to improve language acquisition in patients with minimal verbal language. In this study the authors selected 10 ASD participants (age range 16–21). Post-anodal tDCS of the Broca area, mean vocabulary scores were significantly higher than the pre-anodal tDCS scores.

The studies are suggestive for therapeutic benefits of non-invasive brain stimulation in autistic children. However, due to the small numbers of studies, in which different protocols had effects on different target functions, statements about optimal protocols are premature.

DEPRESSION

Depression in children and adolescents is associated with significant functional disability in multiple environmental realms (Cosgrove et al., 2013). Depression involves a distributed network of cortical and limbic regions, including the DLPFC (especially the left), and subgenual cingulate gyrus, amongst others (Mayberg, 2007). It has been shown (Fitzgerald et al., 2006) that in depression these areas, and specifically the left-hemispherical ones, may be hypoactive, whereas right-hemispheric hyperactivation might take place, thus constituting an hemispheric dysbalance of activation. The rationale of the brain stimulation studies presented here is to increase the activity of the left DLPFC.

Walter et al. (2001) were the first to report the impact of rTMS on depression in 3 patients younger than 18 years. The patients received daily treatment over 2 weeks of 10 Hz rTMS over the left DLPFC. Two participants improved clinically, but one of them complained about tension headache during two of the treatment sessions. In another case report series, Loo et al.

(2006) tested the effect of 10 Hz rTMS upon the left DLPFC over 6 weeks on two 16-year-old adolescent girls affected by depression and ADHD. No improvements of ADHD symptoms, but a reduction of depression symptoms was reported. Bloch et al. (2008) conducted an open label rTMS study with nine adolescents (16–18 age range) affected by severe treatment-resistant depression. Participants received 14 sessions of 10 Hz rTMS to the left DLPFC. Depression scores of the participants improved significantly. Two of them remained in clinical remission 1 year after therapy (as judged by regular clinical follow-up). Five subjects reported mild headaches. No other adverse effects were reported. More recently, Wall et al. (2011) conducted an open-label trial of adjunctive rTMS in eight adolescents with treatment-resistant depression. These subjects were maintained on a stable dose of a selective serotonin reuptake inhibitor (SSRI). All in all, thirty daily 10 Hz rTMS treatments were given over the left dorsolateral prefrontal cortex. The CDRS-Revised mean scores improved significantly from baseline over the course of 30 treatments and the 6-month follow-up. Pre- and post-treatment neurocognitive testing did not reveal any decline in functioning. These data are preliminary as no control group was included, but this study shows that intensive treatment parameters were well tolerated by adolescent patients. No studies for treatment of depression in children have been conducted with tDCS.

The available studies suggest some therapeutic effect of rTMS for the treatment of childhood depression. A recurring element associated with a successful rTMS therapy is the stimulation of left DLPFC at 10Hz. However, since these are open and/or case report studies, the results of these studies should be interpreted with caution.

SCHIZOPHRENIA

Childhood-onset schizophrenia is a rare and severe form of the disorder (Nicolson and Rapoport, 1999), that is neurobiologically and physiologically continuous with adult onset schizophrenia (David et al., 2011). Hallucinations are, probably, the most dramatic clinical symptom that causes significant problems for the life of patients with schizophrenia.

Physiological abnormalities have been reported in several neural regions including right medial temporal, lateral temporal, inferior frontal cortex, and in the cingulate cortex bilaterally, left DLPFC and left superior temporal gyrus (Vyas and Gogtay, 2012; Hayempour et al., 2013). However, neuroimaging studies have shown relatively less predictive value despite consistent reports of progressive structural brain abnormalities associated with schizophrenia. An increase of left temporoparietal cortex excitability is associated with positive symptoms, specifically auditory hallucinations (AHs) (Silbersweig et al., 1995; Shergill et al., 2000). On the other hand, activity enhancement of the left prefrontal region has been suggested to improve negative symptoms (Heimer et al., 1997), due to its effect on the release of dopamine (Strafella et al., 2001). Therefore, excitability-reducing stimulation is proposed to reduce activity of the left temporoparietal cortex, while excitatory non-invasive brain stimulation has been used to increase left prefrontal region activation for therapeutic application (see Freitas et al., 2009; Demirtas-Tatlidede et al., 2013 for a complete review).

Jardri et al. (2007) report a single case study involving a 11-year-old boy with medication-resistant schizophrenia. An fMRI scan displayed increased auditory cortex activity with concurrent AHs. 10 sessions of 1 Hz rTMS were administered to the left temporoparietal cortex. Verbal AHs decreased by 50%. The improvement obtained with rTMS was maintained by repeating the sessions every 5 weeks. No adverse effects of rTMS were reported. More recently, the same group (Jardri et al., 2012) established a case series of adolescents diagnosed with childhood-onset schizophrenia according to the Schedule for Affective Disorders and Schizophrenia for School-Age Children ($n = 10$, 15.5 years old). All participants had frequent and drug-resistant AHs. The patients received 1 Hz rTMS to the T3-P3 site over 5 days. The authors assessed scalp discomfort clinically and describe only minor discomfort. AHRS scores decreased significantly from baseline to the immediate post-treatment assessment, and from baseline to the 1-month assessment. Furthermore, the Global Assessment of Functioning scores improved significantly immediately and 1 month after the treatment, as compared to baseline values.

For tDCS, one study was recently published with regard to childhood-onset schizophrenia (Mattai et al., 2011). This study aimed to investigate the tolerability of tDCS in this patient group. Twelve participants (12 children, age range 10–17) were assigned to one of two groups: bilateral anodal DLPFC stimulation ($n = 8$) or bilateral cathodal superior temporal gyrus (STG) stimulation ($n = 5$). The stimulation protocol consisted of 20 min per day, per 2 weeks. No subjects reported significant discomfort at the electrode sites. However, four individuals had transient redness of the skin under the electrodes that resolved within about an hour after treatment. Although no significant clinical improvement has been reported, this study is the first to demonstrate that tDCS with the applied parameters is well tolerated in adolescents. Complains of fatigue reported by some patients could be related to unspecific effects, such as medication regimens that frequently include the atypical antipsychotic clozapine.

Taken together, knowledge about the effects of non-invasive brain stimulation in childhood onset schizophrenia is still limited. However, the rTMS case reports provided by Jardri et al. hint for some efficacy in reducing hallucinations. The only available tDCS study is in favor for good tolerability of this stimulation protocol. Systematic studies are needed to explore this field to a larger degree.

DISCUSSION

In this work we reviewed the available literature about the effects of non-invasive brain stimulation in pediatric populations (i.e., younger than 18 years) suffering from neuro-psychiatric diseases. We focused our analysis on studies which have examined the therapeutic efficacy of rTMS and tDCS for rehabilitating neurological functions and ameliorating psychiatric syndromes in children.

In general, the studies provide preliminary evidence in support for a therapeutic potential of non-invasive stimulation techniques in children and adolescents. However, several limitations should be taken into account.

Virtually no double-blinded sham controlled studies are available at present, which makes it difficult to make safe statements

Table 1 | rTMS studies in childhood brain diseases.

Studies	Design		Patients		Stimulation protocol						Outcome	
	Sham controlled	Blinding	Disease	Sample size	rTMS intensity	Stimulation position	Number of sessions/ days	rTMS frequency	Total number of pulses/ session	Duration per session	Effects	Side-effects
VASCULAR DISEASES												
Kirton et al., 2008	Yes	Partially	AIS	10	100% rMT	Controlesional motor cortex	1 session per day/8 days	1 Hz	1200	20 min	Grip strength improvement	None
Valle et al., 2007	Yes	Double blind	CP	17	90% rMT	Motor cortex	1 session per day/5 days	5 Hz	1500	N/A	Reduction of spasticity	None
EPILEPSY												
Brasil-Neto et al., 2004	No	Open	Left front-central slow activity	1	95% rMT	Frontal cortex (Epileptogenic focus)	1 session per day/2 sessions per week/3 months	0.3 Hz	100	N/A	No effects	None
Graff-Guerrero et al., 2004	No	Open	EPC	2	50% of the TMS device power (case 1) 128% rMT (case 2)	Frontal cortex (Epileptogenic focus)	1session/1 day	20 Hz	N/A	N/A	Seizure discharge reduction	None
Fregni et al., 2005a,b,c	No	Open	Cortical mal-formation	3	65% of the TMS device power	Epileptogenic focus vs. Cz	1 session/1 day	0.5 Hz	600	20 min	Seizure discharge reduction	None
Morales et al., 2005	No	Open	EPC	2	N/A	Motor cortex (Epileptogenic focus)	2 sessions/1 day (case 1) 2 session/1 day + 1 session (second day-case 2)	Patient 1: 1–6 Hz Patient 2: 1: 1 Hz-6 Hz-1 Hz	N/A	N/A	No effects	None
Kinoshita et al., 2005	No	Pilot	Extratemporal lobe epilepsy	1	90% rMT	PCz	2 sessions per day/5 days in a week	0.9 Hz	N/A	15 min	No effects	None

(Continued)

Table 1 | Continued

Studies	Design		Patients		Stimulation protocol						Outcome	
	Sham controlled	Blinding	Disease	Sample size	rTMS intensity	Stimulation position	Number of sessions/ days	rTMS frequency	Total number of pulses/ session	Duration per session	Effects	Side-effects
ADHD												
Weaver et al., 2008	Yes	Open	ADHD only	4	100% rMT	Right DLPFC	1 session per day/5 days per week/2 weeks	10 Hz	2000 stimuli	N/A	Improved attention in the Sham + active rTMS condition	None
TOURETTE												
Kwon et al., 2011	No	Open	TS only	2	100% rMT	SMA	10 daily sessions/10 days	1 Hz	1200	N/A	Tics reduction	None
Le et al., 2013	No	Open	TS only	25	100% rMT	SMA	1 session per day/5 days per week/4 weeks	1 Hz	1200	20 min	Tics reduction	None
AUTISM SPECTRUM DISORDERS												
Baruth et al., 2010	Control group	Open	Autistic	22	90% rMT	Bilateral DLPFC	1 session per day/1 day per week/12 weeks	•1 Hz	150	N/A	Reduction of irritability and repetitive behavior	None
Sokhadze et al., 2010	No	Open	Autistic	13	90% rMT	Bilateral DLPF cortices	1 session per day/2 day per week/3 weeks	0.5 Hz	150	N/A	Reduced errors % in the oddball task and ritualistic behaviors	None
DEPRESSION												
Walter et al., 2001	No	Open	Unipolar major depression	3	Between 90 and 110% of the rMT	Left DLPFC	1 session per day/5 days per week/2 weeks	10 Hz	1600	N/A	Improvement in 2 cases on 3	Tension headache reported in one case with improvement
Loo et al., 2006	No	Open	Depression/ ADHD comorbidity	2	110% rMT	Left DLPF cortex	1 session per day/5 days per week/6 weeks	10 Hz	40 trains/5 s per train	N/A	Improvement measured with the CDRS	None

(Continued)

Table 1 | Continued

Studies	Design		Patients		Stimulation protocol						Outcome	
	Sham controlled	Blinding	Disease	Sample size	rTMS intensity	Stimulation position	Number of sessions/ days	rTMS frequency	Total number of pulses/ session	Duration per session	Effects	Side-effects
Wall et al., 2011	No	Open	Depression	8	120% MT	Left DLPF cortex	1 session per day/5 days per week over 6–8 weeks	10 Hz	3000	N/A	Improvement measured with the CDRS	None
Bloch et al., 2008	No	Open	Depression	9	80% MT	Left DLPF cortex	1 session per day over 14 days	10 Hz	20 sessions/2 s per trains	20 min	Improvement measured with the CDRS and BDI	None
SCHIZOPHRENIA												
Jardri et al., 2007	No	Open	Schizophrenia	1	100% rMT	left tem-poroparietal cortex	1 time per day/10 days	1 Hz	1000 stimuli	N/A	The Verbal AHs decreased	None
Jardri et al., 2012	No	Open	Schizophrenia	10	90% rMT	T3-P3	2 times per day/5 days	1 Hz	1200 stimuli	N/A	Improvement measured with the CDRS	Minor discomfort

Shown are studies dedicated to the treatment of Vascular diseases, Epilepsy, ADHD, Tourette, Autism Spectrum Disorder, Depression, Schizophrenia in childhood populations. Study characteristics, details of the stimulation protocols as well as effects of stimulation, including side effects, are shown. AIS, Arterial ischemic stroke; CP, Cerebral Palsy; EPC, Epilepsia partialis continua; ADHD, Attention-deficit/hyperactivity disorder. Stimulation targets areas are described according to the international 10-20 system.

Table 2 | tDCS for the treatment of childhood brain disorders.

Studies	Design		Patients	Stimulation protocol							Outcome	
	Sham controlled	Blinding		Polarity	Therapeutic electrode position	Return electrode position	Current strength (mA)	Electrode size (cm^2)	Duration (min)/sessions	Sample	Effects	Side-effects
EPILEPSY												
San-Juan et al., 2011	No	No	Rasmussen's encephalitis	C	F2	F8	2	12 mm in length × 0.4 mm diameter	60 min/4 sessions (on days 0, 7, 30, and 60)	1	Cathodal tDCS improves epilepsy, linguistic, and motor functions	None
Yook et al. (2011)	No	No	Slow waves/ right hemisphere and intermittent spikes/ temporoparietal area	C	Right temporo-parietal area (between P4-T4)	Left orbit	2	25	20 min/5 days per week/2 weeks	1	Cathodal tDCS reduces seizure attacks and duration	None
Varga et al., 2011	Yes	Partially (patients)	($n = 1$) SP, GTP ($n = 1$) CP ($n = 1$) SP, CP, GTP ($n = 1$) Atonic ($n = 1$) CP, GTC	C/S	$N = 1$ T7 $N = 2$ FT7 $N = 3$ T7 $N = 4$ TP8 $N = 5$ T7 On the area of peak negativity	On the area of peak positivity (more widespread)	1	25	20 min/2 sessions/1 day	5	Effect on EEG patterns or clinical symptoms only in 3 patients	None
Auvichayapat et al., 2013	Yes	Partially (statician)	($n = 18$) Idiopathic ($n = 4$) MTS ($n = 2$) FCD ($n = 3$) Others	C/S	Seizure focus	Controlateral shoulder	1	35	20 min (one session)	36	Significant reductions in epileptic discharge frequency immediately and 24 and 48 h after tDCS	None

(Continued)

Table 2 | Continued

Studies	Design		Patients	Stimulation protocol							Outcome	
	Sham controlled	Blinding		Polarity	Therapeutic electrode position	Return electrode position	Current strength (mA)	Electrode size (cm^2)	Duration (min)/sessions	Sample	Effects	Side-effects
AUTISM												
Schneider and Hopp, 2011	No	Partially (statician)	Autism	A	Left DLPFC	Right supraorbital	0.08	25	30 min (one session)	10	Anodal tDCS over left DLPF cortex improved vocabulary score	None
Schizophrenia												
Mattai et al., 2011	Yes	Possibility of open treatment	Schizophrenia	C/A/S	Bilateral anodal DLPFC stimulation ($N = 8$) Bilateral cathodal superior temporal gyrus (STG) stimulation ($n = 5$)	Non-dominant forearm	2	25	20 min/5 days per week/2 weeks	12	None	Tingling ($n = 7$); Itching ($n = 6$)

Shown are studies dedicated to treatment of Vascular diseases, Epilepsy, ADHD, Tourette, Autism Spectrum Disorder, Depression, Schizophrenia in childhood populations. Study characteristics, details of the stimulation protocols as well as effects of stimulation, including side effects, are shown. A, anodal tDCS; C, cathodal tDCS; S, sham tDCS. Stimulation targets areas are described according to the international 10–20 system. Legend: SP, simple partial seizures; GTP, generalized tonic-clonic seizures; CP, complex partial seizures; MTS, Mesial temporal sclerosis; FCD, Focal cortical dysplasia.

about efficacy. Since there seems to be a potential, these studies are urgently needed. Moreover, systematic studies to identify optimal stimulation protocols based on physiology are missing, including comparisons between different protocols, and a systematic evaluation of safety of non-invasive brain stimulation with regard to the developing brain. It is important to note that, although the examined literature does deliver no hint for major adverse effects in children, the evidence currently available is still rather scanty. Studies conducted in adult humans and animal models are probably not transferable one-to-one to children, since anatomy and physiology differs relevantly between these groups (Johnston, 2009). In this regard, it is important to consider that the developing brain is characterized by "sensitive" periods or rather periods during which the effects of the experience on the brain are unusually strong during a limited period in development (Knudsen, 2004). This suggests that, during development, the risk to induce maladaptive neural plasticity due to brain stimulation techniques might be relatively high (Vicario and Nitsche, 2013). Because of this, we suggest that neuroscientists willing to apply non-invasive brain stimulation in children should consider dose-finding studies, and a longitudinal monitoring of neural plasticity triggered by these methods (through neuroimaging and/or electrophysiological techniques), to control for functional and structural changes. In this connection, it will be important to improve knowledge about physiological effects of stimulation in children. This might provide important landmarks for assessing the therapeutic effectiveness of the adopted stimulation protocol as well as the presence of side effects. Moreover, discoveries provided by research in "sensitive" periods at the circuit level might be helpful for this issue as they could supply insights of paramount importance for predicting the trajectories of neural plasticity induced by non-invasive brain stimulation techniques and their related therapeutic results. Worthy of discussion is also the fact that the current state of investigations involving the application of brain stimulation methods in pediatric populations is unbalanced toward TMS (See **Tables 1**, **2** for detailed summaries).

No published studies are currently available with regard to the therapeutic efficacy of tDCS in childhood disorders such as stroke and/or brain injury, TS, ADHD, and Depression. Nevertheless, the interest in applying tDCS for treating pediatric populations is growing.

FUTURE DIRECTION OF RESEARCH

The application of non-invasive brain stimulation for the rehabilitation and/or treatment of children might have the potential advantage of promoting improvements superior to those achievable in adulthood, according to the fact that the developing brain is characterized by "sensitive periods" during which the effects of the experience on the brain are unusually strong for a limited period (Knudsen, 2004). Therefore, the improvement of symptoms via non-invasive stimulation treatment in pediatric age might be more stable, and consistent. However, as discussed above, this same "sensitivity" might also be risky in terms of induction of maladaptive neural plasticity.

In order to minimize this risk, future lines of research should address the following, still limited, field of investigations:

- Exploration, also by using animal models, of the physiological effects of non-invasive brain stimulation in children;
- Systematic exploration of childhood clinical populations to clarify the pathophysiology of the respective diseases, which could be objective to non-invasive brain stimulation. This is important for defining optimal protocols.
- Systematic conduction of "dose-finding," sham-controlled, double-blinded studies, which will provide important information not available from the open studies.

These aspects will help to clarify, at several levels of complexity, the potential therapeutic efficacy of non-invasive brain stimulation in children, delivering a realistic basis for clinical application of such stimulation protocols on a large scale.

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rTMS neuromodulation improves electrocortical functional measures of information processing and behavioral responses in autism

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Objectives: Reports in autism spectrum disorders (ASD) of a minicolumnopathy with consequent deficits of lateral inhibition help explain observed behavioral and executive dysfunctions. We propose that neuromodulation based on low frequency repetitive Transcranial Magnetic Stimulation (rTMS) will enhance lateral inhibition through activation of inhibitory double bouquet interneurons and will be accompanied by improvements in the prefrontal executive functions. In addition we proposed that rTMS will improve cortical excitation/inhibition ratio and result in changes manifested in event-related potential (ERP) recorded during cognitive tests.

Materials and Methods: Along with traditional clinical behavioral evaluations the current study used ERPs in a visual oddball task with illusory figures. We compared clinical, behavioral and electrocortical outcomes in two groups of children with autism (TMS, wait-list group). We predicted that 18 session long course in autistic patients will have better behavioral and ERP outcomes as compared to age- and IQ-matched WTL group. We used 18 sessions of 1 Hz rTMS applied over the dorso-lateral prefrontal cortex in 27 individuals with ASD diagnosis. The WTL group was comprised of 27 age-matched subjects with ASD tested twice. Both TMS and WTL groups were assessed at the baseline and after completion of 18 weekly sessions of rTMS (or wait period) using clinical behavioral questionnaires and during performance on visual oddball task with Kanizsa illusory figures.

Results: Post-TMS evaluations showed decreased irritability and hyperactivity on the Aberrant Behavior Checklist (ABC), and decreased stereotypic behaviors on the Repetitive Behavior Scale (RBS-R). Following rTMS course we found decreased amplitude and prolonged latency in the frontal and fronto-central N100, N200 and P300 (P3a) ERPs to non-targets in active TMS treatment group. TMS resulted in increase of P2d (P2a to targets minus P2a to non-targets) amplitude. These ERP changes along with increased centro-parietal P100 and P300 (P3b) to targets are indicative of more efficient processing of information post-TMS treatment. Another important finding was decrease of the latency and increase of negativity of error-related negativity (ERN) during commission errors that may reflect improvement in error monitoring and correction function. Enhanced information processing was also manifested in lower error rate. In addition we calculated normative post-error treaction time (RT) slowing response in both groups and found that rTMS treatment was accompanied by post-error RT slowing and higher accuracy of responses, whereas the WTL group kept on showing typical for ASD post-error RT speeding and higher commission and omission error rates.

Conclusion: Results from our study indicate that rTMS improves executive functioning in ASD as evidenced by normalization of ERP responses and behavioral reactions (RT, accuracy) during executive function test, and also by improvements in clinical evaluations.

Keywords: TMS, autism, ERP, motor response time, behavioral performance

INTRODUCTION

Autism Spectrum Disorders (ASD) are featured by severe deficits in social communication, social interaction, and restricted, repetitive patterns of behaviors, interests and activities (APA, 2013). Additionally, autistic individuals usually present excessive reactions to the sensory environment such as aversive reactions to visual, auditory, and tactile stimuli. These perception and sensory reactivity abnormalities are found in majority of subjects with ASD affecting their ability to effectively process information (Gomes et al., 2008). In a series of electrophysiological studies conducted by our group we explored specifics of event-related potential (i.e., ERP) reflecting information processing during performance on reaction time (RT) tasks in children with ASD (Sokhadze et al., 2009a, 2012b, 2013a; Baruth et al., 2010c; Casanova et al., 2012) Our studies were aimed to explore the manifestations of the impaired functional connectivity, excessive cortical excitation/inhibition ratio, and deficient executive functioning in ASD by analyzing behavioral performance on attention tasks with dense-array ERP recording. Analysis of ERP components is one of the most informative dynamic methods of investigation and monitoring of information processing stages in the human brain due to the high temporal resolution of this technique. Amplitude and latency of ERP waves at selected topographies reflect both early sensory perception processes and higher-level processing including attention, cortical inhibition, memory update, as well as other cognitive activity processes (Polich, 2007). ERPs provide both a method of studying chronometry of information processing stages and a tool by which to assess the neurobiology of cognitive dysfunctions present in this neurodevelopmental disorder. ERP is a very useful technique to characterize time course and amplitude of cortical responses to stimulation (Jeste and Nelson, 2009). Generally, early exogenous ERPs are believed to reflect sensory processing of a stimulus attributes (Coles and Rugg, 1995; Herrmann and Knight, 2001; Eichele et al., 2005; Folstein et al., 2008), whereas late endogenous ERPs are thought to reflect higher level cognitive processes such as attention, memory trace update, perceptual closure, etc. (Pritchard, 1981; Picton, 1992; Polich, 2003, 2007).

One of our first studies investigated ERPs that index selective attention processes in a visual novelty oddball task in children with autism and an age-matched group of typically developing children (Sokhadze et al., 2010a). The ASD group had excessive magnitude to task-irrelevant visual cues as compared to typically developing children and evidenced a lack of visual target discrimination. In a follow-up investigation we found augmented early cortical responses to novel distracters along with lower accuracy of motor response (MR) in a three-stimuli oddball task with illusory Kanizsa figures (Sokhadze et al., 2013a). We concluded that cortical responses to visual stimulation in autism might be indiscriminative during visual tasks negatively affecting selective attention. Large magnitude of electrocortical activity in response to sensory stimulation may be due to an increased ratio between excitation and inhibition in the cortex of individuals with autism (Casanova et al., 2002a,b; Rubenstein and Merzenich, 2003; Casanova, 2005, 2007). Impaired habituation and normative adaptation to repeated stimuli can be considered as an inhibitory deficit manifested in typical symptoms of autism such as stereotypy, sensory hypersensitivity, deficient social interaction skills, etc.

One of contemporary models of autism, so called "minicolumnar theory of autism" (Casanova et al., 2003, 2006a,b; Casanova, 2005, 2007) is based on neuropathological findings in our laboratory. Autism in this model is associated with cortical neurodevelopmental abnormalities. In brief, the reduced neuropil space (periphery of the minicolumn) reported in autism is the compartment where lateral inhibition sharpens the borders of minicolumns and increases their definition (Favorov and Kelly, 1994a,b; DeFelipe, 1999, 2004). The primary source of for this inhibitory effect may be derived from axon bundles of double-bouquet cells (Favorov and Kelly, 1994a). The axons of double bouquet cells arrange themselves in essentially repeatable patterns varying between 15 and 30 μm wide, depending on the cortical area examined (DeFelipe, 1999). Increases in numbers and types of inhibitory interneurons, as seen in the smaller minicolumns of autistic patients, result in greater diversity and more nuanced modulation of minicolumns. Double-bouquet cells in the peripheral neuropil space of minicolumns provide a "vertical stream of negative inhibition" (Mountcastle, 2003) surrounding the minicolumnar core. Other GABAergic cells in the minicolumn, having collateral projections extending hundreds of microns tangentially, provide lateral inhibition of surrounding minicolumns on a macrocolumnar scale.

The value of each minicolumn's output is insulated to a greater or lesser degree from the activity of its neighbors by GABAergic inhibition in its peripheral neuropil space. This allows for gradations in amplitude of excitatory activity across a minicolumnar field. Rubenstein and Merzenich (2003) have posited that reductions in GABAergic inhibitory activity may explain some symptomatology of autism, including increased incidence of seizures and auditory-tactile hypersensitivity (see also Casanova et al., 2003, 2006a,b). Oblak et al. (2010) found decreased GABA receptors in the cingulate cortex and fusiform gyrus in autism. These results may explain some symptomatology of autism, including increased incidence of seizures and sensory (e.g., auditory, tactile) hypersensitivity (Casanova et al., 2003).

This hypothesis is consistent with findings of reduced minicolumnar peripheral neuropil space in the neocortex of autistics relative to controls (Casanova et al., 2002a,b,d). In this model, a reduction in the peripheral neuropil space would result in smaller minicolumns which would coalesce into discrete, isolated islands of coordinated excitatory activity. There are considerable consequences resulting from the significant reduction of neuropil in minicolumns in autism. Reduced surround inhibition may result in an increase in the ratio of cortical excitation to inhibition and excessive amplification of sensory responses reported by autistic individuals. Several important functions of the prefrontal cortex, for instance executive functions might be affected ability of individuals with autism focus on task-relevant targets without being distracted by task-irrelevant cues (Gray et al., 2003; Folstein et al., 2008; Matzel and Kolata, 2010). There are several reviews describing consequences of

increased excitation-to-inhibition (E/I) ratio both in humans and in animal models (Rubenstein and Merzenich, 2003; Renart et al., 2010; Harris and Thiele, 2011; Pinto et al., 2013). Deficits within the inhibitory elements that surround the cell minicolumn suggest a mechanistic explanation to the I/E imbalance in autism (Casanova et al., 2003). Oscillations and synchronization of pyramidal cells in and across minicolumns are maintained by networks of inhibitory GABAergic interneurons. Local I/E interactions shape neuronal representations of sensory, motor and cognitive variables, and produce local electroencephalographic (EEG) gamma oscillations. The I/E bias caused by faulty pyramidal cell-interneuronal diads provides a receptive scenario to induced gamma frequency and ERP abnormalities in autism.

TMS offers a noninvasive method for altering excitability of the neural circuits and for inducing a functional reorganization of the cortex. We reported positive effects of repetitive transcranial magnetic stimulation (rTMS) in ASD in our pilot studies using shorter (6–12 sessions) rTMS course (Sokhadze et al., 2009b, 2010a, 2012a; Baruth et al., 2010a,b, 2011; Casanova et al., 2012). TMS-based neuromodulation exerts effects on cortical excitability (Maeda et al., 2000; Pascual-Leone et al., 2000, 2002; Frye et al., 2008; Baruth et al., 2010b; Enticott et al., 2010; Sokhadze et al., 2012a; Oberman et al., 2013). It is proposed that that low-frequency (i.e., "slow"') rTMS ($\leq$1 Hz) has inhibitory effects on stimulated cortex (Maeda et al., 2000), whereas high-frequency rTMS (>1 Hz, e.g., 5 Hz, 10 Hz etc.) increases excitability of stimulated cortex (Pascual-Leone et al., 1994, 2000, 2002; Daskalakis et al., 2002; Schutter, 2009; Wassermann and Zimmermann, 2012; Oberman et al., 2013). Probably the effect of low frequency rTMS are mediated through increases in the activation of inhibitory neurons (Hoffman and Cavus, 2002; Wagner et al., 2009). We propose that inhibitory cells such as basket and chandelier interneurons, whose projections keep no constant relation to the surface of the cortex, of the double-bouquet neurons are oriented in more geometrically exact manner and are located at the periphery of the minicolumn and therefore they are more appropriate candidate for induction by a TMS applied parallel to cortex. Low frequency rTMS in autism, may lower the cortical excitation/inhibition ratio, so called E/I ratio index.

In this study we were interested in how rTMS treatment affects specific ERP components known to index processes in sensory cortex, association cortical areas, and areas related to higher level cognitive activity. As it was mentioned above, the exogenous ERPs reflect early-stage, modality-specific, while endogenous ones reflect modality non-specific associative higher order processing of stimuli within the context of the task (Näätänen et al., 1978; Luck et al., 1990; Coles and Rugg, 1995; Hillyard and Annlo-Vento, 1998). Posterior visual P100 are generated within the fusiform gyrus with contribution from parieto-occipital and occipital cortices (Yamazaki et al., 2000). Frontal N100 ERP wave occurs within a similar time window and probably originates from more anterior frontal dipole generators (Clark et al., 1994).

The fronto-central P300 (so called P3a) reflects frontal lobe activity (Friedman et al., 1993) and in a visual oddball task with distracters is interpreted as an attentional "orienting", whereas centro-parietal and parietal P300 (P3b) is believed to reflect sustain attention and other higher level processes. This cognitive ERP component has multiple dipole sources (Townsend et al., 2001).

Negative N200 component is recorded in visual tasks over centro-parietal cortex around 200–300 ms post-stimulus (Näätänen et al., 1978, 1993) and reflects processes of stimulus categorization, perceptual closure and attention focusing signaling that a perceptual representation has been formed (Potts et al., 2004). A frontal positivity with a peak within (P2a, 180–320 ms post-stimulus) over inferior prefrontal recording sites is selectively responsive to the evaluation of the task relevance of presented stimuli, and originates from the orbito-frontal cortex (Potts et al., 1996, 1998, 2008). This frontal component may index task-relevant features of the stimulus (Kenemans et al., 1993). The fronto-central N200 according to some researchers (West, 2003; Donkers and van Boxtel, 2004; West et al., 2004) is thought to originate from the anterior cingulate cortex (ACC) and prefrontal sources and may reflect processes related to potential response conflict detection in a RT tasks and/or cortical inhibition of inappropriate MR. All ERP components have certain variability, but specific ERP measures selected for this study (frontal N100, N200 and P300, and parietal P100, N200 and P300) are less affected by variability in visual tasks and are relevant to the study goal.

We proposed that after 18 sessions of 1 Hz rTMS—administered to the dorso-lateral prefrontal cortices (DLPFC) participants with autism would demonstrate normalization of electrocortical indices of attention both at the early (P100, N100, 100–200 ms post-stimulus) and the late (i.e., P200, N200, P300, 200–600 ms) stages of sensory and cognitive processing and show improvements in MT accuracy. Mainly, we expected lower magnitude and longer latencies to visual targets (i.e., better stimulus discrimination), and attenuated reactivity to non-target illusory figures and other non-target cues. Other anticipated improvements were expected to be found in outcomes of social and behavioral functioning questionnaire and surveys. The hypothesis in this study proposed that low-frequency rTMS (i.e., inhibitory) would exert its effects through increased cortical inhibitory tone (i.e., lower E/I ratio) in the DLPFC with subsequent improvement in performance in the visual attention task. In addition we expected improvements in clinical social and behavioral evaluation outcomes.

METHODS

Participants with ASD (age range 9–21 years) were recruited through the University of Louisville Weisskopf Child Evaluation Center (WCEC). Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000) and further ascertained with the Autism Diagnostic Interview—Revised (ADI-R; Le Couteur et al., 2003). They also had a medical evaluation by a developmental pediatrician. All subjects had normal hearing based on past hearing screens. Participants with a history of seizure disorder, significant hearing or visual impairment, a brain abnormality conclusive from imaging studies or an identified genetic disorder were excluded. Fifty participants were high-functioning persons with autism diagnosis and four had Asperger Syndrome. All had full-scale IQ

>80 assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) or (for adolescents) the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

We enrolled 54 autistic patients, 44 males and 10 females, with a mean age of 14.5 ± 2.9 years. Twenty-seven of them were assigned to active 1.0 Hz TMS treatment (TMS group), while 27 were assigned to the WTL group. Mean age of subjects in the TMS group was 14.8 ± 3.2 years, and 14.1 ± 2.6 years in the WTL group. There was not a significant difference in either age or full-scale IQ between the TMS and WTL groups.

The study complied with all relevant national regulations and institutional policies and has been approved by the local Institutional Review Board (IRB). Participating subjects and their parents (or legal guardians) were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local IRB. The subjects were reimbursed only for participation in two ERP tests ($25/per test). The consent and assent forms approved by the IRB were reviewed and explained to all subjects who expressed interest to participate. All questions were answered before consent signature was requested. If the individual agreed to participate, both she/he and parent/guardian signed and dated the consent or assent form and received a copy countersigned by the investigator who obtained consent.

THREE-STIMULI ODDBALL TASK WITH KANIZSA FIGURES

The stimuli employed in the test were Kanizsa square (target), Kanizsa triangle (non-target), non-Kanizsa square, and non-Kanizsa triangle (standards) (Kanizsa, 1976). The task represents a classic three-stimuli oddball with infrequent illusory Kanizsa target (square, 25%) and infrequent Kanizsa distracter (triangle, 25%) figures presented for 250 ms among frequent non-Kanizsa stimuli (so called standards, 50%) with inter-trial interval in 1,100–1,300 ms range (**Figure 1**). Totally 240 trials were presented following a brief practice block. The practice block had 20 trials only with the experimenter present in the room to make sure that subject correctly understands test conditions and recognizes target stimuli. The total time of the test including sensor application and practice was under 30 min. For better habituation and adaptation to experimental setting, the participants were encouraged to have at least one session for conditioning to brainwave sensor net (without performing task) and getting familiar with laboratory environment.

EVENT-RELATED POTENTIAL ACQUISITION AND PROCESSING

Electroencephalographic (EEG) signals from 128 sites were recorded with a dense-array EGI system (Electrical Geodesics, Inc., Eugene, Oregon). Subjects were placed in electrically and acoustically isolated camera from the Industrial Acoustics Co. (Bronx, NY). Stimulus presentation and MT collection was controlled using E-prime (PST, Inc., Pittsburg, PA). Visual stimuli were presented on a flat monitor located in 45–50 cm from the subject, and MTs were registered with a keypad (Serial Box, Inc). Sampling rate of EEG was 500 Hz, and analog Notch (60 Hz, infinite impulse response (IIR)) and analog elliptical bandpass filters were set at 0.1–200 Hz. Impedances were under 40 KΩ. Stimulus-locked EEG data were segmented off-line into 200 ms pre-stimulus baseline to 800 ms epoch post-stimulus. EEG recordings were screened for artifacts and trials with eye blinks, gross movements etc were removed using EGI software artifact rejection tools (Perrin et al., 1987; Fletcher et al., 1996; Srinivasan et al., 1998; Luu et al., 2001). The remaining artifact-free EEG data for trials with correct responses was digitally filtered using Notch filter (IIR, 5th order) and 0.3–20 Hz IIR elliptical bandpass filter. Averaged ERP data was baseline corrected (200 ms) and ERPs after averaging and baseline correction were re-referenced into an average reference frame. Response-locked EEGs were segmented into 500 ms pre-response to 500 ms post-response (i.e., commission error). More detailed account for experimental procedure and EEG data acquisition and processing can be found in our prior publications that used similar methodology (Baruth et al., 2010a,b; Casanova et al., 2012; Sokhadze et al., 2012a,b).

EVENT-RELATED POTENTIALS (ERP)

STIMULUS-LOCKED DEPENDENT ERP VARIABLES

Dependent variables for the frontal and fronto-central region-of-interest (ROI) were N100 (80–180 ms), N200 (220–350 ms), P2a (180–320 ms), and P3a (300–600 ms), and for the parietal and parieto-occipital ROI were P100 (120–180 ms), N200 (180–320 ms) and P3b (320–600 ms) ERP waves. For P2d component (i.e., differences wave of frontal P2a) we calculated difference wave (P2a to targets minus P2a to non-targets) to detect mean difference between two conditions both in amplitude and latency within 180–320 ms post-stimulus window.

RESPONSE-LOCKED EVENT-RELATED POTENTIALS (ERN/Pe)

Response locked dependent variables in this study were amplitude and latency of the Error-related Negativity (ERN peaking within 40–150 ms post-error) and Error-related Positivity (Pe, peaking within 100–300 ms post-error). The ROI for both ERN and Pe components included FCz, sites between FCz and FC3-C1, and between FCz and FC2-C2. Amplitude and latency analysis of ERN/Pe was performed with a custom-made application in Matlab (Clemans et al., 2011a). Validation of correct identification of ERN and Pe waves was further ascertained using another custom Matlab application using wavelet transformation (Clemans et al., 2011b).

TRANSCRANIAL MAGNETIC STIMULATION

Repetitive TMS was administered using a Magstim 220 device (Magstim Corp., Sheffield, UK) with a 70-mm figure-eight coil. Threshold of MT was identified for each hemisphere in all participants with autism by increasing the output of the stimulator by 5% until a 50 μV deflection or a visible twitch in the First Dorsal Interosseous (FDI) muscle was detected in at least 3 trials of stimulation over the motor cortex controlling the contralateral FDI. Electromyographic (EMG) responses were recorded with a C-2 J&J Engineering Inc multichannel physiological monitoring device with Physiodata software (J&J Engineering, Inc., Bainbridge Island, WA).

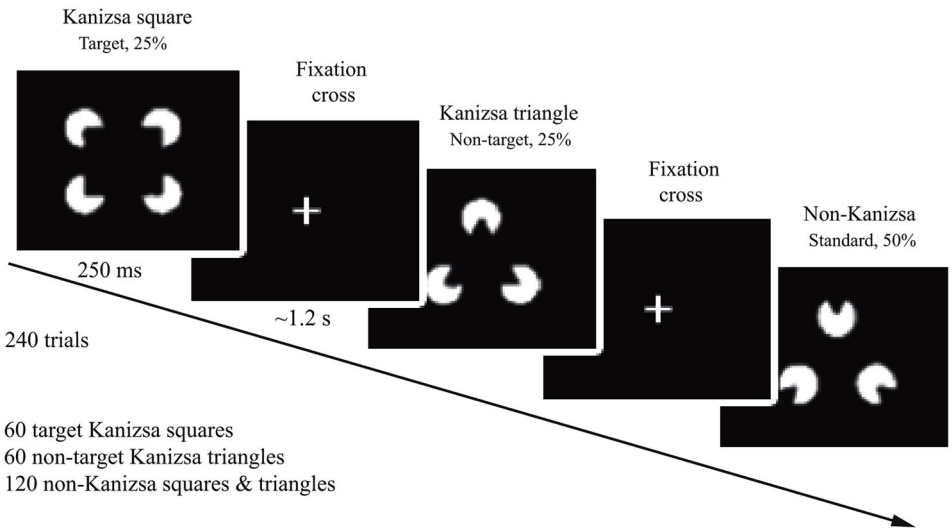

FIGURE 1 | Three-stimuli category visual oddball task with Kanizsa illusory figures. The stimulus types are: Kanizsa square (target, 25%), Kanizsa triangle (25%), non-Kanizsa square, and non-Kanizsa triangle. The non-target Kanizsa triangle is introduced to differentiate processing of Kanizsa figures and targets. The stimuli consist of either three or four inducer disks, which are considered the shape feature, and they either constitute an illusory figure (square, triangle) or not (collinearity feature).

The rTMS was administered weekly for 18 weeks with the 1st six treatments were over the left DLPFC, while the next six were over the right DLPFC, whereas remaining six treatments were done bilaterally over the DLFC (evenly at the left and right DLPFC). The DLPFC site for magnetic stimulation was found by placing the TMS coil 5 cm anterior, and in a parasagital plane, to the site of maximal FDI response. A swimming cap was used to make the TMS coil positioning easier. TMS was administered at 1.0 Hz frequency and 90% MT. There were total of 180 pulses per day session with nine trains with 20 pulses each. There were 20–30 s between the train intervals used. Decision to select 90% of the MT was based on the prior publications where rTMS was used for the stimulation of DLPFC in various neuro- and psychiatric disorders (reviewed in Pascual-Leone et al., 2000; Wassermann and Lisanby, 2001; Daskalakis et al., 2002; Gershon et al., 2003; Loo and Mitchell, 2005; Greenberg, 2007; Oberman et al., 2013).

CLINICAL SOCIAL AND BEHAVIORAL EVALUATION OUTCOMES

For the evaluation of social and behavioral functioning we utilized caregiver reports and clinician ratings of improvement. Every participant was evaluated before TMS course and within 2 weeks following TMS treatment. *Aberrant Behavior Checklist* (ABC; Aman and Singh, 1994; Aman, 2004) is a clinician administered rating scale to assess Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech based on parent/caregiver report. *Social Responsiveness Scale (SRS)*. *Repetitive Behavior Scale—Revised* (RBS-R; Bodfish et al., 1999) is a caregiver completed rating scale assessing stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted range (Bodfish et al., 2000).

STATISTICAL ANALYSIS

The primary model for statistical analyses of subject-averaged ERP and MT data was the two factor repeated measure ANOVA. Dependent ERP variables were amplitude and latency of ERP at pre-determined ROIs. The within-participant factors were followings: *Stimulus* (Kanizsa target, Standard, Kanizsa Non-target), *Hemisphere* (Left, Right), and *Time* (Baseline, Post-treatment). The between-subject factor was *Group* (TMS, WTL). *Post hoc* analyses were conducted where appropriate. RT, error rate (commission, omission and total error rate), were analyzed using *Time* and *Group* factor. For clinical behavioral rating scores a *Treatment* (pre-vs. post-TMS/or waiting period) ANOVA was completed to determine changes associated with active stimulation and WTL conditions. Histograms with normal distribution curves along with skewness and kurtosis data were obtained for each dependent variables to determine normality of distribution and appropriateness of data for ANOVA and *t*-tests. For more reliable determination of normality of distribution residual plots (i.e., normal probability plot, histogram, vs. fits and order) were created using Minitab statistical package to indicate that treatment with ANOVA is justified. All dependent variables in the study had normal distribution. Greenhouse-Geisser corrected *p*-values were employed where appropriate in all ANOVAs. *A priori* hypotheses were tested with the Student's *t*-tests for two groups with equal variance. Confidence intervals (95% of mean, 95% CI) were calculated for each ERP data sets

entered for *t*-tests. For the estimation of the effect size and power (Murphy and Myors, 2004) we used Partial Eta Squared (η^2) and observed power computed using $\alpha = 0.05$. SPSS 19.0 and Sigma Stat 3.1 statistical packages were used for analysis of data.

RESULTS

BEHAVIORAL RESPONSES (REACTION TIME AND ACCURACY, POST-ERROR RT)

Reaction Time (RT)

Effects of TMS on RT to targets were not significant. Comparison of RT to targets yielded no *Time* X *Group* effects.

Accuracy

Commission and omission errors analysis yielded a significant between-group difference in the commission error percentage, $F_{(1,52)} = 4.32$, $p = 0.042$. *T*-test showed significant decrease of commission error rate in the TMS group (mean decrease $-6.38 \pm 2.54\%$, 95% CI from -11.61 to -1.15%, $t_{(26)} = 2.50$, $p = 0.019$). We could not find between group differences in omission error rate. Total error rate (% errors) change also showed decrease only in TMS group ($-7.47 \pm 2.82\%$, 95% CI from -13.26 to -1.67%, $t_{(26)}=2.64$, $p = 0.013$).

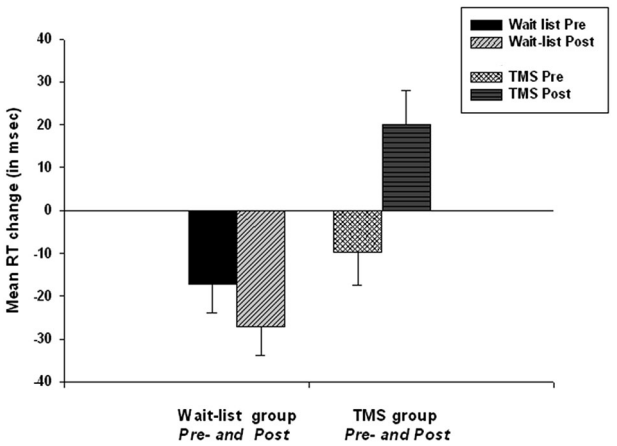

FIGURE 2 | Post-error reaction time (RT) changes in TMS and wait-list groups at the baseline and at the second test. *Time* X *Group* effect is highly significant ($F = 8.05$, $p = 0.006$). At the baseline both groups showed post-error RT speeding, while post-TMS post-error RT became positive. Change of the post-error RT in TMS group was significant ($t = 4.57$, $p < 0.001$).

Post-error RT

Main effect of *Time* (Pre, Post) on normative post-error RT slowing was highly significant ($F_{(1,50)}$=15,14, $p = 0.001$, $\eta^2 = 0.134$, observed power = 0.795 at alpha (α) = 0.05).

Repeated measure ANOVA of post-error RT slowing revealed that TMS and WTL group differences on post-error RT changes were also statistically significant, i.e., *Time* X *Group* interaction, $F_{(1,52)} = 8.05$, $p = 0.006$, $\eta^2 = 0.134$, observed power = 0.795. The TMS group showed post-error RT increase with significant positive change in post-error RT. This change was computed as post TMS post-error RT change minus pre-treatment post-error RT change (49.9 ± 55.4 ms, 95% CI from 26.42 to 69.41 ms, $t_{(26)} = 4.57$, $p < 0.001$). **Figure 2** shows that at the baseline both in WTL and TMS groups post-error RT was negative (mean post-error speeding was -23.1 ± 34.7 ms and not different between groups at pre-treatment stage), while in the TMS group post-error RT became positive (i.e., showed normative slowing), whereas it remained negative in the WTL group.

PARIETAL AND PARIETO-OCCIPITAL ERP COMPONENTS

P100

TMS course had main effects on P100 component's both amplitude ($F_{(1,52)} = 4.78$, $p = 0.033$) and latency ($F_{(1,52)} = 15.00$, $p = 0.001$). Response of this parietal and parieto-occipital P100 component (positive peak within 130–160 ms post-stimulus) to targets showed post-treatment between group difference in amplitude (2.25 ± 2.93 μV, with 95% CI from 1.14 to 3.37 μV, in TMS vs. 4.37 ± 3.89 μV, 95% CI from 2.83 to 5.91 μV, in WTL, $F_{(1,52)} = 5.31$, $p = 0.025$) and latency (153.3 ± 43.99 ms, 95% CI from 136 to 170 ms in TMS vs. 128 ± 18.42 ms, 95% CI from 121 to 135 ms in WTL, $F_{(1,52)} = 7.54$, $p = 0.008$). Group differences in response to Kanizsa targets and non-targets were more expressed in the latency of the P100 ($F_{(1,52)} = 4.91$, $p = 0.011$). The *Stimulus* (Standard, Non-target Kanizsa, Target Kanizsa) X *Time* (Pre, Post) X *Group* (TMS, WTL) effect was significant ($F_{(2,52)} = 4.34$, $p = 0.015$), and this effect was even more powerful for standard vs. target stimuli comparison ($F_{(1,52)} = 7.92$, $p = 0.007$, $\eta^2 = 0.128$, observed power = 0.789). The effect can be described as a reduced latency to non-targets and increased latency to target stimuli post-TMS but not after wait period. There were no hemispheric differences observed for P100 component.

N200

There were no group differences in amplitude of the parietal N200 component. Latency of N200 to targets showed post-treatment between group difference in latency to targets (238.72 ± 58.58 ms, 95% CI from 215 to 261 ms, in TMS vs. 201.35 ± 24.27 ms, 95% CI from 191 to 210 ms, in WTL group, $F_{(1,52)} = 9.34$, $p = 0.004$) and non-target illusory Kanizsa figures (242.31 ± 62.42 ms, 95% CI from 217 to 267 ms, in TMS vs. 208.27 ± 24.92 ms, 95% CI from 198 to 218 ms, in WTL group, $F_{(1,52)} = 6.92$, $p = 0.011$). ANOVA analysis of the latency of parietal N200 to target and non-target Kanizsa stimuli showed a *Stimulus* (Target, Non-target) X *Time* (Pre, Post) X *Group* (TMS, WTL) interaction, $F_{(2,52)} = 3.69$, $p = 0.032$. The effect was expressed as increased latency for non-target stimuli in the TMS group post-treatment. There were observed other interactions as well, for instance hemispheric one, as the effect was featured by more delayed latency at the right hemisphere in the TMS group ($F_{(1,52)} = 7.15$, $p = 0.01$, $\eta^2 = 0.121$, power = 0.747). Other notable interaction was significant *Time* X *Group* effect, $F_{(1,52)} = 4.60$, $p = 0.037$, $\eta^2 = 0.08$, observed power = 0.558, with TMS showing more prolonged N200 latency to non-target Kanizsa stimuli. *Post hoc*

tests showed that in the active treatment group latency increased (e.g., to non-targets, bilaterally 24.2 ± 11.8 ms, 95% CI from 3.7 to 51.0 ms, $t_{(26)} = 2.37$, $p = 0.025$) along with attenuated amplitude (−1.39 ± 3.26μV, 95% CI from −2.63 to −0.15 μV, $t_{(26)} = 2.30$, $p = 0.029$), while changes of latency and amplitude of N200 in the WTL group were not significant (see **Figure 3**).

P300 (P3b)

We found between group differences in P3b amplitude that were expressed as more attenuated component post-treatment in TMS as compared to WTL group only to non-Kanisza standards (2.69 ± 2.96 μV, 95% CI from 0.88 to 3.61 μV, in TMS vs. 5.09 ± 3.98 μV, 95% CI from 3.21 to 6.14 μV, in WTL, $F_{(1,52)} = 5.25$, $p = 0.026$). We found no interactions of P3b amplitude using in ANOVA *Stimulus*, *Hemisphere, Time*, and *Group* factors. *Stimulus* (Target, Non-target Kanisza, Standard) factor had a main effect on latency of P3b ($F_{(2,53)} = 11.59$, $p < 0.001$). The latency of P3b showed significant effects of *Time* factor on each stimuli: latency of P3b to targets, 364.15 ± 63.08 ms, 95% CI from 340 to 380 ms, in TMS vs. 326.13 ± 28.27 ms, 95% CI from 314 to 337 ms, in WTL, $F_{(1,52)} = 8.16$, $p = 0.006$; non-target Kanizsa, 356.68 ± 67.26 ms, 95% CI from 333 to 384 ms, in TMS vs. 322.93 ± 21.55 ms, 95% CI from 314 to 331 ms, in WTL, $F_{(1,52)} = 6.94$, $p = 0.011$; and standards, 354.89 ± 64.68 ms, 95% CI from 330 to 379 ms, in TMS vs. 323.54 ± 20.68 ms, 95% CI from 315 to 331 ms, in WTL, ($F_{(1,52)} = 5.25$, $p = 0.026$). Repeated measure ANOVA analysis of the P3b latency also indicated a significant between groups differences for all types of illusory figures, for example, increased P3b latency as a result of rTMS (*Time* × *Group* interaction, $F_{(1,52)} = 4.32$, $p = 0.044$), that can be described as a longer post-treatment latency in TMS, shorter in WTL group.

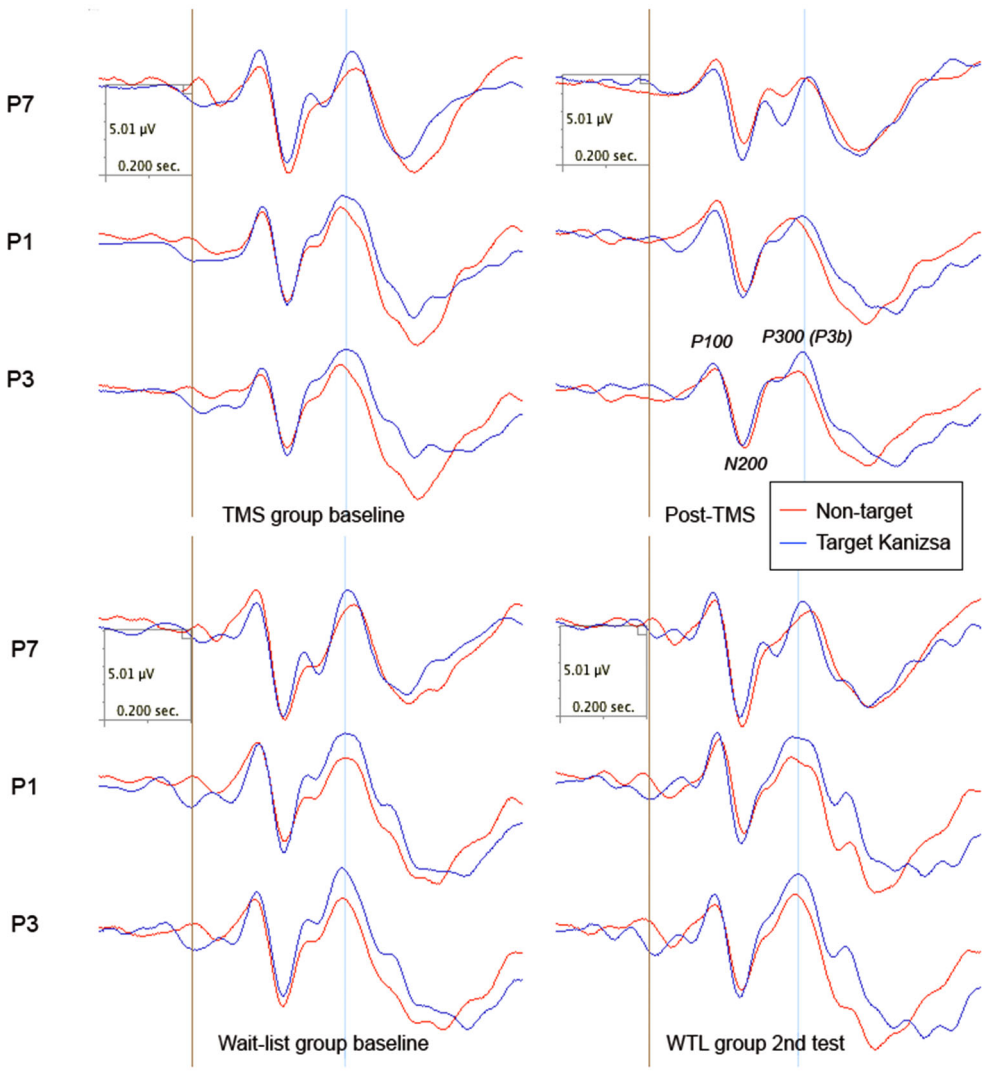

FIGURE 3 | Parietal ERPs (P1, P3, P7 sites according to 10–10 International System) to target and non-target Kanizsa figures in TMS and wait-list groups (*N* = 27/per group) before and after treatment (TMS/or wait-period).

FRONTAL AND FRONTO-CENTRAL ERP COMPONENTS

N100

Comparison of post-treatment amplitude and latency of N100 ERP component showed decreased amplitude and prolonged latency to both target and non-target Kanizsa figures in the TMS group, while N100 magnitude was practically unchanged in the WTL group. Effects of *Time* factor on amplitude and latency to targets was significant (at post-TMS test, amplitude, −1.54 ± 1.83 μV, 95% CI from −2.72 to −0.88 μV, in TMS vs. −2.91 ± 2.96 μV, 95% CI from −3.59 to −1.74 μV, in WTL, $F_{(1,52)}$ = 4.62, p = 0.036; while latency, 140.85 ± 32.76 ms, 95% CI from 127 to 153 ms, in TMS vs. 120.83 ± 20.87 ms, 95% CI from 112 to 129 ms, in WTL group). Effects of *Time* on frontal N100 to non-targets was also statistically significant (amplitude, −1.36 ± 1.63 μV in TMS vs. −2.37 ± 2.07 μV in WTL, $F_{(1,52)}$ = 4.47, p = 0.04; latency, 140.59 ± 23.22 ms in TMS vs. 125.4 ± 13.38 ms in WTL, $F_{(1,52)}$ = 8.58, p = 0.005). There were no interaction of N100 amplitude and latency on *Stimulus*, *Hemisphere* and *Group* factors.

N200

There was observed significant between *Group* (TMS, WTL) difference in N200 amplitude ($F_{(1,52)} = 8.24$, $p = 0.006$, $\eta^2 = 0.119$, observed power = 0.804). A *Stimulus* (Target Kanizsa, Non-Kanizsa standard) X *Hemisphere* (Left, Right) X *Group* (TMS, WTL) interaction reached significance ($F_{(1,52)} = 4.64$, $p = 0.037$) pointing at a more negative N200 to targets with less negative N200 to non-target Kanizsa as a result of rTMS (**Figure 4**). The TMS group showed less hemispheric differences post-treatment, while the WTL group had more negative amplitude of N200 at the right hemisphere. A *Time* X *Group* effect for

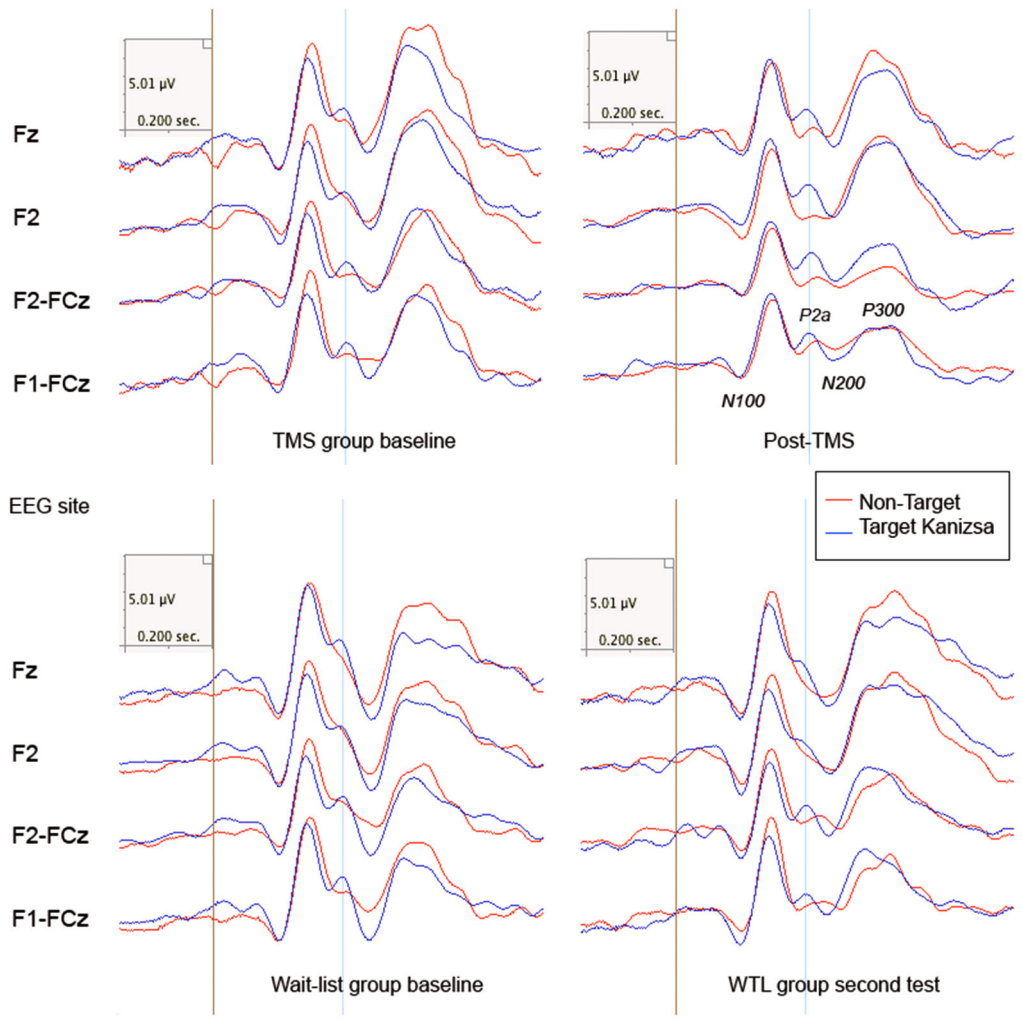

FIGURE 4 | Frontal and frono-central ERPs (Fz, F2, F2-FCz, F1-FCz) to target and non-target Kanizsa figures in TMS and wait-list groups (*N* = 27/per group) before and after treatment (TMS/ or wait-period). Frontal P2a components (280–320 ms post stimulus) is marked with a blue line.

the latency of N200 was significant ($F_{(1,52)}$ = 7.26, p = 0.009, η^2 = 0.119, observed power = 0.754), yielding longed latency to targets post-TMS. Additionally, *post hoc* analysis using *t*-test showed that N200 latency became statistically more prolonged to target stimuli in TMS group across both hemispheres (13.31 ± 34.03 ms, 95% CI from 26.2 to 0.36 ms, $t_{(26)}$ = 2.10, p = 0.044).

P2d

The frontal P2a calculated as a mean difference between P2a amplitude to target Kanizsa minus P2a amplitude to non-target Kanizsa stimuli. TMS had significant effect at P2d amplitude ($F_{(1,52)}$ = 6.56, p = 0.013). The baseline values in both groups were similar (−2.35 μV in TMS vs. −2.51 μV in WTL) but showed significant difference post-treatment (1.34 ± 4.65 μV in TMS vs. −1.97 ± 3.56 in WTL group). ANOVA showed significant *Time* X *Group* interaction, $F_{(1,52)}$ = 4.11, p = 0.048, η^2 = 0.075, observed power = 0.512. Effect can be described as P2d becoming positive post-TMS, i.e., P2a component to targets was larger than to non-targets. Paired sample *t*-test confirmed that P2d amplitude increased significantly post-TMS (3.70 ± 7.47 μV, 95% CI from 6.71 to 0.68 μV, $t_{(26)}$ = 2.52, p = 0.018). Differences in P2d latency between groups were not significant (**Figure 5**).

P300 (P3a)

The treatment had main effect on the amplitude of the frontal P300 (P3a) component ($F_{(1,52)}$ = 4.27, p = 0.044). The amplitude of P3a showed a *Time* X *Group* effect that was statistically significant ($F_{(1,52)}$ = 4.64, p = 0.036). The active TMS showed post-treatment decrease of the P3a bilaterally across all stimuli, whereas WTL group showed no differences at all. Paired sample *t*-test showed that decrease of the amplitude in TMS group was significant both for non-target Kanizsa (−1.93 ± 3.09 μV, 95% CI from −0.54 to −3.33 μV, $t_{(26)}$ = 2.85, p = 0.008) and target Kanizsa stimuli (−2.91 ± 3.84 μV, 95% CI from −0.64 to −5.18 μV, $t_{(26)}$ = 2.64, p = 0.014). There were not detected any main effects or interactions in the latency of the frontal P3a.

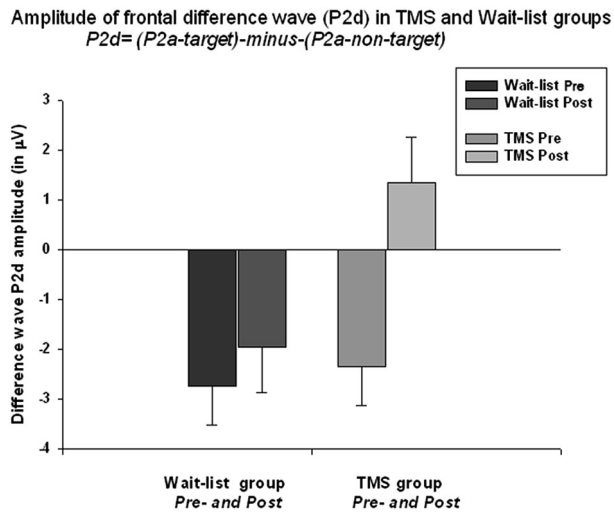

FIGURE 5 | Amplitude of the frontal P2a difference wave (so called *P2d = [P2a to targets minus P2a to non-targets]*) across both hemispheres shows *Time* X *Group* interactions effect (*F* = 4.11, *p* = 0.048). Difference wave (P2d) was negative at the baseline in both groups (i.e., lower amplitude to targets as compared to non-targets), but becomes positive post-TMS. Increase of P2d was significant in the TMS group (t = 2.52, p = 0.018).

RESPONSE-LOCKED FRONTAL AND FRONTO-CENTRAL ERN AND Pe

Two subjects did not show sufficient number of commission errors and were excluded from the analysis. TMS and WTL groups showed significant differences in ERN amplitude ($F_{(1,50)}$ = 6.20, p = 0.016) and latency ($F_{(1,50)}$ = 5.82, p = 0.023). Amplitude of ERN during commission errors across five frontal and fronto-central sites showed marginal *Time* X *Group* interaction ($F_{(1,50)}$ = 4.05, p = 0.05), and paired-sample *t*-test showed significant increase of ERN negativity in the TMS group (by 2.97 ± 3.21 μV, 95% CI from 0.36 to 4.60 μV, $t_{(26)}$ = 2.40, p = 0.023, see **Figure 6**). Analysis of ERN latency ANOVA yielded statistically significant *Time* X *Group* effect, ($F_{(1,50)}$ = 4.24, p = 0.041, η^2 = 0.099, observed power = 0.55). *T*-test of the ERN latency changes in the TMS group showed significant decrease (−28.1 ± 13.8 ms, 95% CI from −4.22 to −52.1 ms, $t_{(24)}$ = 2.41, p = 0.023). Amplitude and latency of Pe wave in both groups were not significantly changed post-treatment. **Figure 7** shows ERN and Pe waveforms in two groups at the first (baseline) and at the second test.

CLINICAL BEHAVIOR EVALUATIONS POST-TMS

We found a significant decrease in stereotype repetitive and restricted behavior patterns following 18 sessions of bilateral rTMS as measured by the RBS-R (Bodfish et al., 1999) and analyzed them using a paired sample Student's *t*-test. Total RBS-R score decreased from 23.4 to 19.1, mean decrease being

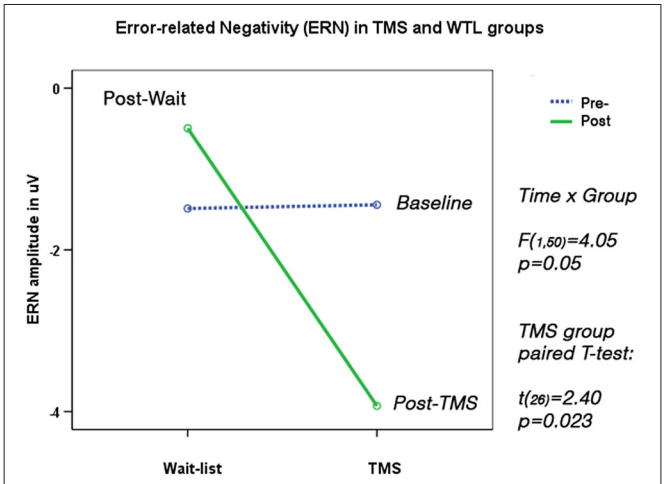

FIGURE 6 | Error-related Negativity (ERN, 40–120 ms post-error) shows *Time* X *Group* interaction (*F* = 4.05, *p* = 0.05). Post-TMS ERN amplitude became significantly more negative (t = 2.40, p = 0.023). N = 26/per group, as 2 subjects out of 54 committed no commission errors on the second test.

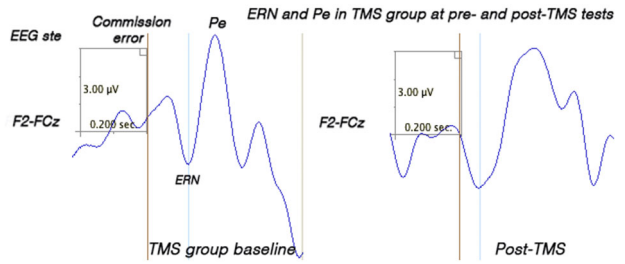

FIGURE 7 | Error-related Negativity (ERN) and Positivity (Pe) from the fronto-central midline EEG sites. Grandaverage waveforms at the fronto-central site (between F2 and FCz, *N* = 26 per group) show more negative amplitude and shorter latency of the ERN in the TMS group post-treatment. ERN peak occurring within 40–140 ms post-error is marked by a blue line.

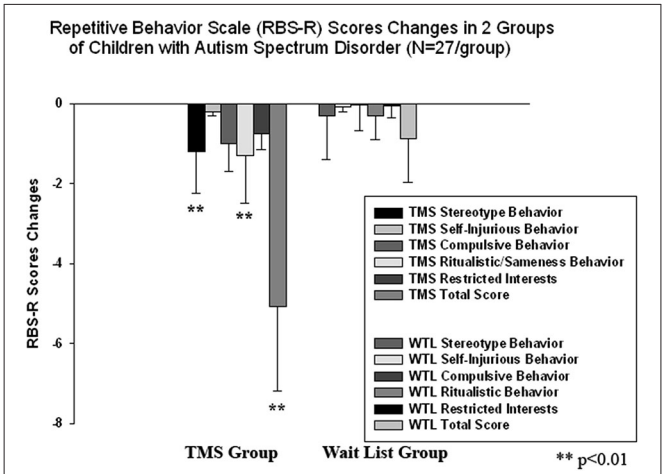

FIGURE 8 | Changes of Repetitive Behavior Scale (RBS-R) scores post-TMS/wait-list treatment as compared to baseline levels in two groups of children with ASD (*N* = 27/per group). Stereotype Behavior, Ritualistic Behavior and Total RBS scores decreased significantly in the TMS group.

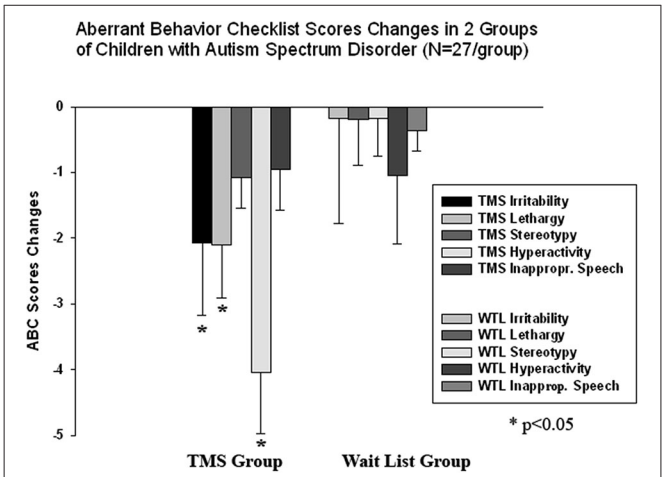

FIGURE 9 | Changes of Aberrant Behavior Checklist (ABC) scores post-TMS/wait-list treatment as compared to baseline levels in two groups of children with ASD (*N* = 27/per group). Irritability, Lethargy, and Hyperactivity rating scores decreased significantly post-TMS.

−4.29 ± 5.9, 95% CI from −1.95 to −6.63, $t_{(26)}$ = 6.63, p = 0.001. Changes in individual subscale scores is depicted at the **Figure 8**, where both Stereotypic Behavior subscale and Ritualistic/Sameness behavior subscale scores show significant decrease (accordingly −1.00 ± 1.77, 95% CI from −0.28 to −1.71, $t_{(26)}$ = 2.89, p = 0.008 and −1.33 ± 2.21, 95% CI from −0.45 to −2.21, $t_{(26)}$ = 3.12, p = 0.004). There was identified as well a significant reduction in Irritability subscale as measured by the ABC (Aman and Singh, 1994), i.e., −2.07 ± 5.12, 95% CI from −0.40 to −4.10, $t_{(26)}$ = 2.10, p = 0.045. Lethargy and Hyperactivity subscales showed even more pronounced score reductions (Lethargy, −2.11 ± 3.93, 95% CI from −0.51 to −3.72, $t_{(26)}$ = 2.71, p = 0.012; Hyperactivity, −4.03 ± 7.68, 95% from −0.99 to −7.07, $t_{(26)}$ = 2.72, p = 0.011). Changes of individual subscale rating scores in TMS group are depicted at the **Figure 9**. The WTL group had no significant differences in any of RBS-R or ABC scale ratings as a result of the waiting period.

DISCUSSION

Our results show significant changes in behavioral responses (accuracy, post-error RT slowing) and both early and later-stage ERP indices of task-relevant signal processing as a result of 18 sessions of low frequency rTMS treatment course in children with ASD.

Participant in TMS group showed decreased amplitude and prolonged latency of parietal P100 and N200 components to all stimuli, more for non-target cues. Parietal P3b ERP component was also prolonged without amplitude change in TMS group. In our prior study (Sokhadze et al., 2009b, 2010a, 2013b) at the parietal and parieto-occipital cortices the autism group showed significantly prolonged latency of N100 and reduced amplitude of N200 to targets as compared to neurotypical controls. Latency of the P3b was longer to distracters, without any amplitude group difference to targets and novels. The ASD group had prolonged latencies to novels but not to targets, with effect being better expressed in the right hemisphere. The results indicate the excess of efforts needed for the differentiation of targets from non-target novels in individuals with ASD. TMS treatment enhanced the process of target recognition during performance on task. Especially informative in this regard was positive change of the frontal P2d difference wave that indicates increase of P2a component to target Kanizsa stimuli vs. non-target Kanizsa stimuli, thus reflecting easier discrimination of target features of the stimuli (illusory square vs. illusory triangle).

In addition, at the same frontal topography N200 component was more negative to targets as compared to non-target illusory figures and had longer latency resulting in globally higher magnitude of N200 to targets. Following TMS course the N200 component at the frontal sites became more negative to targets, and at the same time significantly less negative to both types of non-target stimuli. The positive frontal P2a component followed

by the negative ERP N200 component (both of them peaking within 280–320 post-stimulus) in visual oddball tests tasks are associated with categorization, perceptual closure and attention focusing ultimately signaling that a perceptual representation has been formed (Potts et al., 2004). This wave is enhanced if the presented stimulus contains a feature or attribute defining the target in the task according to Potts et al. (2004). It was previous reported (Sokhadze et al., 2009a; Baruth et al., 2010c) that individuals with ASD as compared to typical controls showed enhanced N200 to task irrelevant as compared to task relevant stimuli, and the finding that N200 became more negative to target Kanizsa figures and less negative to non-target distracters post-rTMS treatment indicates a trend to normalization of the response pattern pointing at an improved visual signal processing and a more effective discrimination of the target.

The results indicate a reduction of the frontal P3a both to target and non-target stimuli post-TMS in our ASD patients. In our earlier studies comparing ASD and typical controls we reported that the ASD group showed prolonged N100, P100, and P3b to targets stimuli, emphasizing a change indicative of abnormalities of sustained attention compared to controls. At the same time, the ASD group exhibited a prolonged P3a to novels, and this can be considered as a marker of impaired orientation to novelty, and ultimately decreased frontal associative and integrative functioning. In the current study our results show no differences in amplitude, though the latency of the P3a was still delayed.

Over-activation in the parietal cortex at the early stages of processing of non-targets, either standards or infrequent distracters, and at the same time under-activation of integrative frontal regions at the late stages of target processing was found to occur in autism in a similar visual task that was using three-stimuli paradigm with rare novel distracters (Sokhadze et al., 2009b, 2010a). Our results in a series of visual oddball tasks indicated enhanced and prolonged early frontal ERPs and a delayed late P3a to non-target stimuli, which would suggest low selectivity in pre-processing and at a later stage under-activation of integrative regions. Overall, this is an indication of an over-connected network where sensory inputs evoke abnormally large evoked potentials for unattended stimuli such as frequent standards and rare novel distracters at all stages of visual signal processing with signs of a reduced selectivity of the activation.

The results of the current study indicate that rTMS may have facilitated attention and target discrimination by improving conflict resolutions during processing task-relevant and task-irrelevant stimuli. The latency of posterior P3b was prolonged to targets but reduced to both non-target Kanzisa and non-Kanizsa stimuli following rTMS. The P3b has been linked to task-relevance and the decision- related character of the stimulus as it indicates memory-updating and individual trial processing closure (Picton, 1992). Earlier we (Sokhadze et al., 2009a,b, 2012b) noted that individuals with autism showed prolonged P300 peak to irrelevant distracters as compared to typical controls, which was similar to effects reported by other groups (Courchesne et al., 1989; Townsend et al., 2001). The auditory and visual sensory information processing abnormalities been described in ASD by different researchers (Kemner et al., 1994, 1999; Bomba and Pang, 2004). However, most of these studies analyzed and reported outcomes of late cognitive potentials such as centro-parietal P3b (Courchesne et al., 1989; Ciesielski et al., 1990) and frontal P3a (Townsend et al., 2001). There are only a few papers reporting short latency ERP components' differences in individuals with autism. Majority of these studies emphasize over-activation as well as an abnormal pattern of basic perceptual processes such as low selectivity regardless of modality, abnormal top-down attentional control including delayed attentional orienting to novel stimuli, and deficits in information integration processes (Belmonte and Yurgelun-Todd, 2003). In typically developing children the fronto-central P3a occurs earlier in time as compared to parietal P300 (P3b), but in autistic subjects the P3a and P3b components were found to peak almost simultaneously over the frontal and parietal sites in a spatial attention test (Townsend et al., 2001). The latency of P3a is thought to be associated with the speed of attentional orienting to significant novel stimulus and reflects working memory processes in the prefrontal cortex. Centro-parietal P3b is usually described as a cognitive component that indexes context update and closure. This cognitive potential was found to be delayed but was not significantly attenuated in the group of children with autism as compared to typical controls (Sokhadze et al., 2009a,b, 2010a, 2012b).

The results of the study may indicate facilitation of visual target discrimination processes and enhanced habituation to task-irrelevant distracters post-TMS. We report significant improvement in the accuracy of MTs, lower total error rate and improved normative post-error RT slowing following 18 session long rTMS course. These result support our earlier findings outlining improvement in attention, executive control, and irrelevant response inhibition post-TMS treatment in autism.

In our initial rTMS pilot studies (Sokhadze et al., 2009b, 2010a) we used only six sessions of low frequency rTMS applied only to the left DLPFC and assessed behavioral performance in a visual attention task in children with autism. In a very similar manner, our current study also found a notable reduction in the frontal N200 and altered latency of the parietal P3b to task-irrelevant stimuli. Additionally, similar to the present investigation we also found a significant reduction in the response errors rate following a shorter courses of the prefrontal rTMS (Sokhadze et al., 2009b, 2012a; Baruth et al., 2010a). It might be stated that we found even more pronounced changes in cognitive ERPs such as P2d, N200and P3b in this study that had the greater number of rTMS treatments (18 sessions). In another study using this time 12 sessions of rTMS we found a significant reduction in repetitive and restricted behavior patterns as well as a significant reduction in irritability according to clinical and behavioral questionnaires (Casanova et al., 2012).The results of current 18 session-long rTMS treatment confirm and expand our prior findings of reduced repetitive behaviors (Sokhadze et al., 2009a,b, 2010a,b; Baruth et al., 2010b) and irritability (Baruth et al., 2010a,b) following low-frequency rTMS course. It should be noted that we found significant reductions in irritability only as a result of 12 sessions of bilateral stimulation (Baruth et al., 2010a), whereas reductions in repetitive behavior have been

significant after six sessions of stimulation to the left DLPFC (Sokhadze et al., 2009b, 2010a).

It was a very reasonable decision to select DLPFC as a site for rTMS stimulation. The DLPFC processes components of working memory, decision making process, and regulates the ability to focus attention on task-relevant goals while inhibiting responses to distracters (Gray et al., 2003; Enriquez-Geppert et al., 2010; Matzel and Kolata, 2010). Suggested disruption in the ratio between cortical excitation and inhibition especially within the prefrontal cortex in individuals with autism (Casanova et al., 2002a, 2006a,b) was confirmed in individuals with Asperger syndrome (Casanova et al., 2002c). Reduced cortical inhibitory tone and an increased E/I ratio could adversely affect patterns of cortical activation, possibly resulting in isolated islands of coordinated excitatory activity and in a high comorbidity rate of ASD and epilepsy (Tuchman and Rapin, 1997). We believe that a course of 18 neuromodulatory sessions of low frequency rTMS may restore the cortical E/I balance by selective activation of double-bouquet cells at the periphery of cortical minicolumns (Casanova et al., 2006a,b; Casanova, 2007). It was shown that minicolumnar abnormalities in autism are most significant within the prefrontal cortex, more specifically, the DLPFC and the ACC (Fernandez-Duque et al., 2000; Mesulam, 2000; Casanova et al., 2002b, 2006a,b).

Rubenstein and Merzenich (2003) put forward a hypothesis that at some forms of autism could be caused by a disproportionate high level of excitation (E) or disproportionately weak inhibition (I) resulting in a high E/I ratio. Cortical circuits with such enhanced E/I level are proposed to be featured by poor functional differentiation which may lead to broad-ranging abnormalities in perception, memory and cognition, and motor control. Among other defects, individuals with autism have well known perceptual processing abnormalities, including a hypersensitivity to auditory, visual and tactile stimulation (Gomot et al., 2002; Plaisted et al., 2003). Studies of perceptual systems in animal models may provide useful insights into mechanisms underlying sensory disturbances in autism. In particular, investigations of auditory development in rats using modulated noise manipulation showed that the representation of sound inputs in the cortex remains poorly differentiated when the cortex is undergoing development under very poor signal-to-noise conditions (Chang and Merzenich, 2003). The E/I balance in the cortex is controlled by the relative numbers and functional activity of glutamatergic and GABA-ergic neurons. Neurodevelopmental abnormalities may lead to increased number, morphology or functional balance of excitatory vs. inhibitory neurons and can lead to a hyper-excitable state typical for autism. Excessive noise in cortical structures processing information also negatively affects development of normally differentiated representations. Relatively undifferentiated representations of orienting signals or significant stimuli would result in larger and less selective response. Such over-representation by non-differentiated responses could account for the strong aversive reactions to auditory, tactile and visual stimuli that are common in autism.

Casanova et al. (2003) study indicated that minicolumns in the brains of individuals with autism are narrow and have altered internal organization. More specifically, their minicolumns have less peripheral neuropil space, which is the conduit for inhibitory local circuit projections. A defect in these GABAergic interneurons may correlate with the increased E/I balance and prevalence of seizures among autistic patients. The authors concluded that GABAergic interneurons are vital for sensory signal processing (e.g., filtering capacity, proper signal discrimination, etc.), thus providing a putative correlate to autistic symptomatology. As it was noted in a recent review on use of TMS in ASD (Oberman et al., 2013), TMS could be particularly informative in detecting abnormalities in E/I ratios in ASD given theoretical studies regarding role of GABAergic interneurons in autism etiology (Hussman, 2001) and specifically role of high E/I balance in autism (Casanova et al., 2003; Rubenstein and Merzenich, 2003). Our current study is supportive of idea that rTMS is capable to improve E/I ratio as manifested in electrocortical responses to sensory stimulus processing in visual selective attention test.

This TMS study was guided by the "minicolumnar" theory of autism. The hierarchical basis of the modular organization of the cerebral cortex is well recognized in the literature. The cerebral cortex originates during brain development as germinal cells from the ventricular and later on the subventricular zones divide asymmetrically and the resulting neuroblasts migrate towards the pial surface (for review see Casanova and Trippe, 2006). The migrating neuroblasts split the preplate to form the incipient cortex wherein arriving cells acquire an orderly inside-out configuration by using either somal translocation or radial glia projections as a scaffold (Marín-Padilla, 1998). The resulting vertical arrangement of cells within this dynamic system serves as an attractor for satellite interneurons to populate its peripheral neuropil space. Radially migrating neurons provide for future pyramidal cells while those that follow a tangential path, primarily from the ganglionic eminences, are destined to be interneurons. Different types of interneurons form dyadic units with pyramidal cells and the resulting ensemble of cells, along with their afferent/efferent projections, constitute information processing units better known as minicolumns (Marin-Padilla, 2010). Recent studies indicate that higher cognitive functions including our executive functions derive from the workings of these modules or minicolumns (Opris et al., 2013).

Topographical studies of minicolumnar morphometry in ASD have shown the greatest deviance from neurotypicals within the prefrontal cortex (Casanova et al., 2002d, 2006a, 2010). Some investigators have explained this fact as resulting from the prolonged maturation time of this structure which thus provides a larger time window of opportunity for exogenous factors to alter its development (Opris and Casanova, 2014). Within the rostral brain region abnormalities within the DLPFC could serve as a pathological correlate to observed executive function deficits in autism (Opris and Casanova, 2014). Given the vertical orientation of inhibitory elements within the periphery of the minicolumns (e.g., double bouquet cells) it has been proposed that rTMS in ASD could preferentially help build the inhibitory surround of these modular structures. Since the dorsolateral prefrontal cortex has been a source of significant minicolumnopathy in published postmortem studies it could be viewed as a target for stimulation using rTMS (Casanova et al., 2002b, 2012). Furthermore,

considering the trans-synaptic effects of rTMS, the large number of DLPFC connections could provide a therapeutic cascading effect in other parts of the brain. In autism computerized image analysis suggests the presence of a minicolumnopathy characterized by an increased density of modules and a diminution in their peripheral neuropil space (Casanova et al., 2002a). The deficits previously described by our group have been corroborated using a variety of neuronomorphometric techniques (e.g., Euclidean minimum spanning tree, gray level index), in an independent sample conducted by an international study where the investigators were blind to the study variables, and in the published results of other investigators (Casanova et al., 2002d, 2006a; Buxhoeveden et al., 2006). The diminished width of the minicolumnar peripheral neuropil space is seen throughout laminae II-VI, suggesting a deficit of an anatomical element in-common to all layers (Casanova et al., 2010). Since inhibitory elements populate all layers of the lateral compartment of the minicolumn pathology involving these elements could contribute to a deficit in the lateral or peripheral inhibitory surround of these modules. These findings gain credence from EEG recordings using lateral masking paradigms and threshold studies using flutter stimuli that sustain the presence of a lateral inhibitory deficit in autism (Kéïta et al., 2011; Puts et al., 2014). It is plausible to propose that low frequency rTMS is increasing inhibitory tone and improving lateral inhibition, and this may result in an enhancement of executive functions.

Executive function deficits were always in the center of attention in autism research. Executive function of behavioral performance monitoring comprises error detection and response conflict monitoring, functions that can be measured using response-locked ERPs such as ERN and Pe (Gehring et al., 1993; Carter et al., 1998; Van Veen and Carter, 2002; Mars et al., 2005; Arbel and Donchin, 2009, 2011). The ERN is a well-studied component whose parameters were investigated under different experimental task conditions, and its ties to error processing have been well established (Carter et al., 1998; Falkenstein et al., 2000; Gehring and Knight, 2000; Van Veen and Carter, 2002). There is an increased number of research studies examining ERN during commission errors in children (Davies et al., 2004). It is established that executive functions normally improve with age (Huizinga et al., 2006) along with demonstration that the ACC, which is now associated with executive performance monitoring, undergoes important maturation changes from childhood into adolescence, and then into adulthood (Arbel and Donchin, 2009, 2011). Furthermore, the studying error processing maturation can be used to understand mechanisms of various neurodevelopmental disorders, such as ADHD and ASD, which feature impairments in execute control (Liotti et al., 2005; Vlamings et al., 2008; Zhang et al., 2009; Sokhadze et al., 2010b). The ERN abnormalities are interpreted as reflecting early error processing impairments. A number of studies have investigated the functional relationship between the ERN and the fronto-central stimulus-locked N200, while some suggest that they represent distinct neurophysiological processes (Ridderinkhof et al., 2004), others suggest they represent different time points of the same process of response conflict monitoring (Yeung and Cohen, 2006).

One of the most important findings of current study was replication of the increase of ERN amplitude and shortened latency post-TMS reported in previous study using 12 sessions of rTMS (Sokhadze et al., 2012a). In accord with our previous study (Sokhadze et al., 2012a), the Pe component did not change post-TMS. This component has a more posterior topography and is expressed as a positivity elicited after the ERN (Falkenstein et al., 2000; Nieuwenhuis et al., 2001; Overbeek et al., 2005). In our earlier study with rTMS application in ASD (Sokhadze et al., 2009a,b, 2010a; Baruth et al., 2010c) we found that most of EEG changes such as ERP and evoked EEG gamma frequency oscillations occurred at the early stages of visual stimulus processing (e.g., less than 200 ms post-stimulus), and resulted in a better discrimination of target from non-target stimuli. Facilitation of target recognition following TMS treatment and more effective early inhibition of non-target distracters leads to less pronounced carryover of non-target over-processing. We suggested earlier that more expressed positive neuromodulation effects in the early ERPs rather than in the late ERPs might be due to enhanced suppression of task- irrelevant stimuli and less effortful discrimination of targets from non-targets during attention task performance.

One more critical methodological issue to be considered in absence of significant TMS effects on Pe in autism might be related to the number of commission errors as this measure depends on the actual number of committed errors (Franken et al., 2007). It is feasible to suggest that the magnitude of the Pe was affected by the reduced number of commission errors in active TMS group. Our prior investigation of ERN/Pe complex in autism (Sokhadze et al., 2010b) also did show Pe differences between ASD and typical children on the similar visual oddball task, but these differences were found only in a form of a significantly prolonged latency of the Pe in ASD group. There is a possibility of a dissociation of ERN and Pe effects since generation of Pe wave might be affected by the absence of feedback about the accuracy of the MR resulting in that lower awareness of error (Hewig et al., 2011).

In general, our findings are in concordance with a recent review of rTMS applications in autism research and treatment (Oberman et al., 2010, 2013). In that review the authors concluded that, though results of published studies are promising suggesting that specific rTMS protocols (Enticott et al., 2010, 2012, 2013; Fecteau et al., 2011) targeting selected regions of cortex may lead to improvement in behavioral deficits in some individuals with ASD, the therapeutic results have been still of preliminary character and additionally, the large-scale, controlled trials necessary to establish the safety and efficacy these neuromodulation protocols have to be conducted (Oberman et al., 2010, 2013).

Some limitations to the study should be taken into account. It is often reported in rTMS studies that effects of magnetic stimulation usually do not wash out in approximately one week. We believe that switching to once per week session regimen, (e.g., Casanova et al., 2012; Sokhadze et al., 2012a) improved our protocol and resulted in better clinical outcome measures. Probably the length of staying in the rTMS treatment rather than intensity is one of the main keys of behavioral and electrocrtical

improvements that we observe in our later rTMS trials in ASD (Baruth et al., 2010b, 2011; Sokhadze et al., 2010a, 2012a; Casanova et al., 2012). It should be recognized that the power (90%) and schedule (number of magnetic pulses delivered per each session, 10–20 s break between trains, etc.) of our rTMS is relatively lower than those used by other TMS treatment protocols. However, it must be mentioned that other known TMS protocols were targeting psychopathologies such as treatment-resistant major depression, or neurological disorders such as for instance Parkinson disease in adults. One more limitation of the study is the use a waiting-list group as a control group rather than using a randomized clinical trial (RCT) design with a sham rTMS condition. Even though our group has a custom-made sham Magstim TMS coil and interface enabling blinding of TMS delivery, we considered this study as a preliminary pilot with a WTL group design, and plan to consider progression to a RCT design on the future stages. It is possible to consider as a limitation also the difficulty of proving in non-invasive human brain research that low frequency rTMS is activating primarily double-bouquet inter-neurons. We hope that future neurophysiological studies on animal models would be able to find support for our hypothesis.

In conclusion, the study showed that treatment with "slow" rTMS improved ERP indices of attention to targets, reduced over-reactivity to non-targets, significantly reduced MT errors to target stimuli, and enhanced response-locked potentials reflective of error monitoring and correction (e.g., ERN to commission errors, post-error RT slowing, etc). We also found significant reductions in both repetitive and stereotypic behaviors, reduced repetitive behaviors, hyperactivity and irritability scores according to social and behavioral clinical evaluations post-TMS. We consider that it is possible to conclude that neuromodulation using low frequency, inhibitory rTMS improved executive functioning and behavior in autism. This study provides further support to the statement that TMS can be regarded as a perspective treatment targeting core symptoms of ASD such as executive function deficits.

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Treatment of visuospatial neglect with biparietal tDCS and cognitive training: a single-case study

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Symptoms of visuospatial neglect occur frequently after unilateral brain damage. Neglect hampers rehabilitation progress and is associated with reduced quality of life. However, existing treatment methods show limited efficacy. Transcranial direct current stimulation (tDCS) is a neuromodulatory technique, which can be used to increase or decrease brain excitability. Its combination with conventional neglect therapy may enhance treatment efficacy. A 72-year-old male with a subacute ischemic stroke of the right posterior cerebral artery suffering from visuospatial neglect, hemianopia, and hemiparesis was treated with biparietal tDCS and cognitive neglect therapy in a double-blind, sham-controlled single-case study. Four weeks of daily treatment sessions (5 days per week, 30 min) were started 26 days post-stroke. During week 1 and 4 the patient received conventional neglect therapy, during week 2, conventional neglect therapy was combined once with sham and once with real biparietal tDCS. Week 3 consisted of daily sessions of real biparietal tDCS (1 mA, 20 min) combined with neglect therapy. Outcome measures were assessed before, immediately after, as well as 1 week and 3 months after the end of treatment. They included subtests of the Test for Attentional Performance (TAP): covert attention (main outcome), alertness, visual field; the Neglect-Test (NET): line bisection, cancelation, copying; and activities of daily living (ADL). After real stimulation, covert attention allocation toward left-sided invalid stimuli was significantly improved, and line bisection and copying improved qualitatively as compared to sham stimulation. ADL were only improved at the 3-month follow-up. This single-case study demonstrates for the first time that combined application of tDCS and cognitive training may enhance training-induced improvements in measures of visuospatial neglect and is applicable in a clinical context.

Keywords: transcranial direct current stimulation, visuospatial neglect, rehabilitation, cognitive therapy, stroke

INTRODUCTION

Neglect is a higher-order, supramodal cognitive deficit, which affects space-related behavior not caused by an elementary sensorimotor deficit (Kerkhoff, 2001), and is mainly caused by lesions in frontoparietal cortical and subcortical networks (Doricchi et al., 2008). Symptoms are heterogeneous and are expressed in different sensory-spatial modalities (visual, auditory, tactile, olfactory). Visuospatial neglect occurs in over 40% of right brain-lesioned patients and in 20% of left brain-lesioned patients (Ringman et al., 2004) and more than 60% of the patients remain impaired after the end of rehabilitation (Carod-Artal et al., 2000; Clarke et al., 2002). Importantly, visuospatial neglect also limits the success of other neurorehabilitative interventions, such as physical and occupational therapy.

Treatment options to date show limited efficiency (Bowen et al., 2013) despite being time-intense. They mostly aim to compensate (e.g., optokinetic stimulation or neck muscle vibration) or substitute functions (e.g., prism adaptation), and few aim to restitute functions (e.g., mental imagery). In the clinical setting, different therapeutic approaches are often combined and individually adapted to the needs of each patient.

In the past decade researchers started to investigate the use of non-invasive brain stimulation in the treatment of neglect. The rationale for using brain stimulation for patients with neglect is based on the "hemispheric rivalry model" proposed by Kinsbourne (1987, 1993). According to this model allocation of visuospatial attention toward both hemifields is balanced by mutual transcallosal inhibition, where each hemisphere competes to direct attention to the contralateral hemifield. Brain

lesions disturb this balance, and while the unimpaired hemisphere becomes hyperexcitable, the impaired hemisphere experiences a reduction in excitability. Supporting evidence for this model was first presented by Vuilleumier et al. (1996). They described a patient who suffered from visuospatial neglect after a stroke affecting the right angular gyrus, which however improved after a second stroke affecting the left frontal eye fields. Both of these areas are important for shifting attention via connections with subcortical structures, moreover supporting the assumption of a widespread network subserving spatial attention.

Later studies using brain stimulation methods further supported Kinsbourne's model. Non-invasive brain stimulation methods can be applied to either increase brain excitability in the lesioned hemisphere or reduce hyperexcitability in the unlesioned hemisphere. Several groups applied repetitive transcranial magnetic stimulation (rTMS) during a single session (Oliveri et al., 2001; Koch et al., 2008), or over several days (Brighina et al., 2003; Shindo et al., 2006; Song et al., 2009; Lim et al., 2010; Kim et al., 2013), with the latter leading to improvements for up to 2–6 weeks after the end of treatment. Two studies reported symptom improvement after a single session of transcranial direct current stimulation (tDCS) (Ko et al., 2008; Sparing et al., 2009). Generally, studies using multiple sessions of TMS showed stronger effects that lasted over a longer period of time.

Diagnostic guidelines for neglect are limited (e.g., Duncan et al., 2005; Intercollegiate Stroke Working Party, 2008) and recommend a multidisciplinary diagnostic approach. In order to diagnose visuospatial neglect, various diagnostic tools should be combined with clinical observation, as individual deficits vary greatly between patients. Covert attention measures provide a sensitive tool to assess the impact of visuospatial neglect and are used as the main outcome measure for this study. Posner et al. (1984) stressed the importance of the parietal lobe in covert attention processes, specifically the disengagement operation, when the target is located in the contralateral hemifield. Furthermore, alertness functions are known to draw on a right-lateralized fronto-parietal network (Sturm and Willmes, 2001; Jäncke et al., 2003) and improvements in alertness are thought to contribute to neglect recovery. Alertness was therefore used as a control parameter. We furthermore applied more traditional tests such as line bisection, cancelation, and copying and furthermore assessed visual field deficits and ADL.

The rational to use bilateral tDCS in this study is based on Kinsbourne's interhemispheric rivalry model and the hypothesis that concurrent biparietal modulation would have a stronger and longer-lasting impact on interhemispheric balance than unilateral stimulation. Biparietal stimulation (anode right, cathode left) was applied to concomitantly increase brain excitability in the lesioned right posterior parietal cortex (PPC) and reduce hyperexcitability in the unlesioned left PPC. Furthermore, we hypothesized that combining stimulation with conventional neglect therapy could have synergistic effects and therefore enhance treatment efficacy.

To our knowledge, this is the first study to report the combined impact of repeated biparietal tDCS sessions and cognitive neglect therapy on rehabilitation outcome.

MATERIALS AND METHODS

PATIENT

We studied a 72-year-old, ambidextrous male who was admitted to the neurorehabilitation unit 23 days after the onset of a moderate ischemic stroke (NIHSS 11/42) of the right posterior cerebral artery of unknown etiology (TOAST 5). At admission he suffered from a left-sided hemiparesis of the arm and face, hemianopia, and severe neglect symptoms. Structural magnetic resonance imaging showed extensive lesions within the right hemisphere affecting mostly subcortical areas of the temporal, parietal and occipital lobe (**Figure 1**).

Neglect symptoms included sensory as well as motor components (directional hypokinesia). Visuospatial symptoms were more space- than object-centered and N.H. showed a gaze deviation toward the right. Imaginary spatial representation was well preserved as compared to his reduced exploratory-perceptional performance. Alertness performance was initially reduced and fluctuating. Furthermore, impairments in spontaneous speech functions (finding words, dysarthria), and a moderate impairment of verbal and non-verbal memory functions, as well as executive functions (inhibitory control, cognitive flexibility) were observed. On discharge, 12 weeks after stroke onset, he had improved attention allocation toward the left hemi-space, however, transfer to activities of daily living (ADL) was limited, specifically in situations with many external distractors. Executive functions and non-verbal memory improved during rehabilitation but were still impaired at discharge. Verbal memory as well as speech functions normalized. N.H. gave written and oral consent according to the Declaration of Helsinki (1964). Family members were informed about all study procedures and approved of his participation. The protocol was approved by the local ethics committee.

STUDY DESIGN

This double-blind, sham-controlled single-case study consisted of 4 weeks of daily treatment sessions (5 days per week, 30 min) starting 26 days post-stroke (**Figure 2**). During week 1 and 4 the patient received conventional cognitive neglect therapy, during week 2, conventional therapy was combined once with sham tDCS and once with real biparietal tDCS. Week 3 consisted of daily sessions of real biparietal tDCS (1 mA, 20 min) combined with neglect therapy and covert attention was measured immediately after every session. Outcome measures were assessed before and after baseline (week 1), single stimulation sessions (week 2), repeated stimulation sessions (week 3), as well as 1 week and 3 months after the end of treatment. After the end of combined treatment, the patient received 7 more weeks of standard neurorehabilitative care before being discharged from the hospital. Assessors and the patient were blinded with regards to stimulation protocols. During the 4-week treatment N.H. furthermore attended occupational (daily), physical (daily), and music therapy (twice per week).

ASSESSMENTS

Covert attention, alertness (intrinsic and phasic), and visual field were assessed with subtests of the Test for Attentional Performance (TAP 2.2, Zimmermann and Fimm, 2002). The

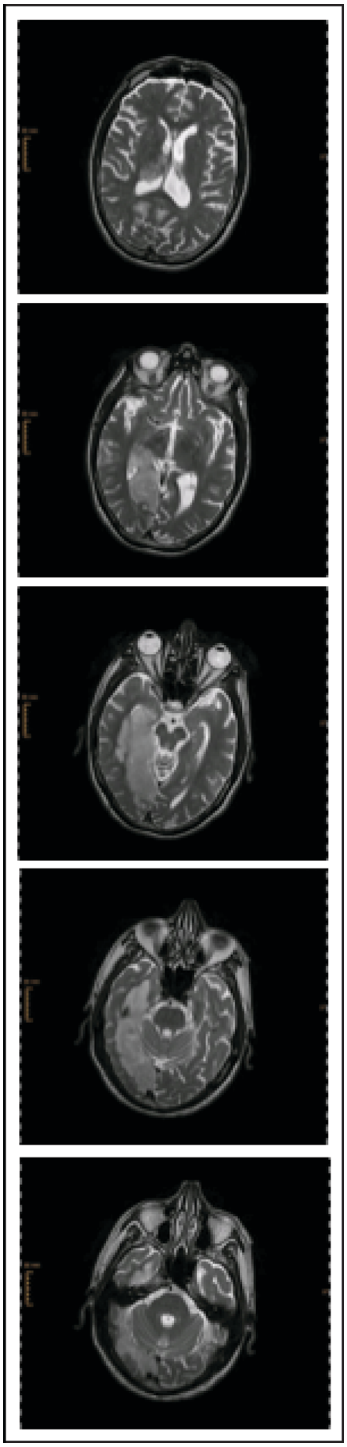

FIGURE 1 | sMRI T2 after admission to acute hospital.

subtests to assess intrinsic and phasic alertness consist of simple reaction paradigms that require keystrokes as selective reactions to non-verbal stimuli (cross displayed in the middle of the screen). Intrinsic alertness measures the general alertness of the subject, while phasic alertness measures the ability to increase and maintain attention in expectancy of a stimulus. The subtest "Covert Attention" measures the ability to direct visual attention toward a stimulus without change of gaze direction (Posner, 1980) and is a sensitive measure of visual neglect. A central cue (arrow) indicates the side on which a target stimulus (cross) may appear (presentation time of 2 s). The arrow either points in the direction of where the stimulus appears (valid trials) or in the opposite direction (invalid trials). As in invalid trials attentional focus is initially shifted in the opposite direction, re-orientation is needed. Visuospatial neglect is indicated by prolonged reaction times (RTs) in invalid trials toward the contralesional hemi-field. RT to invalid left-sided stimuli was therefore the main outcome measure. Visual field deficits were assessed with the subtest "Visual Field." In this test peripheral flicker stimuli appear on a black screen (with fixation control) and the subject indicates with a keystroke whether it was perceived.

Line bisection, cancelation, and copying figures were assessed with subtests of the Neglect-Test (NET, Fels and Geissner, 1996), which is a German adaptation of the "Behavioral Inattention Test" (BIT, Wilson et al., 1987). In order to control for transfer effects on ADL, a questionnaire to measure visuospatial disorders (Beobachtungsbogen für räumliche Störungen, BRS, Neumann and Kerkhoff, 2007) was filled out by the occupational therapist and a family member. It measures impairments in ADL such as eating, self-care, dressing, and communication. Furthermore, side effects of tDCS were assessed with a questionnaire.

TREATMENT

Computerized training batteries (OK-Neglect: Psycware, Sulzbach-Rosenberg, Germany; RehaCom: Schuhfried GmbH, Moedling, Austria) were presented on a large screen (ca. 1.5×2 m) with the patient seated on the right side of the screen. Training was started 5 min after the onset of stimulation and continued for 30 min. Therapies were adapted to the patient's individual needs according to best clinical practice. The main focus was on amelioration of smooth pursuit eye movements (SPEM) and training of saccades toward the neglected hemi-field, as well as visual exploration and reading combined with optokinetic stimulation.

Direct current of 1 mA was delivered for 20 min via two saline-soaked sponge electrodes (7×5 cm), which were fixed on the head with a rubber bandage (NeuroConn DC-stimulator, Eldith, Electro-Diagnostic and Therapeutic Systems GmbH, Ilmenau, Germany). The anode was placed over P4 and the cathode was placed over P3 (international 10–20 EEG system). The current intensity used in this study has been used in several publications with stroke patients (Fregni et al., 2005; Hummel et al., 2005, 2006; Hummel and Cohen, 2005; Boggio et al., 2007). In order to achieve comparable sensations for sham stimulation, all sessions started with a slow up-ramping of current over 30 s. At the end of the stimulation current was turned off slowly in order not to elicit perceptions (Gandiga et al., 2006).

ANALYSIS

The TAP provides norms for adults (TAP 2.2, Zimmermann and Fimm, 2002). Significance levels of intraindividual single-subject differences of *T*-values for the used subtests (intrinsic and phasic alertness, covert attention) were calculated with the software

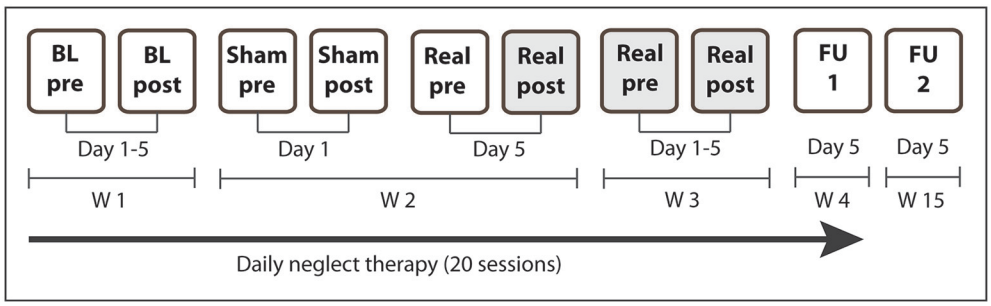

FIGURE 2 | Study design. N.H. received daily standard cognitive neglect therapy for 4 weeks (20 sessions). During W1 the patient received standard therapy only (5 sessions). During W2 the patient additionally received sham tDCS on the first day and real biparietal tDCS on the fifth day. During W3 the patient additionally received real biparietal tDCS (5 sessions) and covert attention was assessed after each session. Post-stimulation measures of day 5 (Real post) served as pre-measures for FU1 and FU2. During W4 he received standard therapy only (5 sessions, FU1). Long-term outcome was assessed 3 months after the end of the stimulation (FU2). BL, baseline assessment; FU, follow-up; W, week. Shaded cells depict real stimulation.

CASE123 (Willmes, 1985, 1990; Guillot and Willmes, 1993) using *T*-values (percent ranks transformed into standard values), test–retest reliability, and subtest correlations. CASE123 is used to perform psychometric single-case analyses according to Huber (1973), which are based on the classical test theory model and are used for tests with standard norms from large standardization samples with satisfactory reliability estimates such as the used TAP. We compared performance pre- vs. post each single session (Sham 1, Real 1, Real 1/5), pre vs. post repeated sessions (Real 5/5), pre vs. post the 1-week control period (FU1), as well as pre vs. post the 3-month control period (FU2). Post-stimulation measures (Real 5/5) served as pre-measures for FU1 and FU2. Paper-pencil test results (line bisection, cancelation, figure copying) are described qualitatively.

In order to evaluate whether coupling stimulation with cognitive training was more effective than cognitive training alone, a $2 \times 4 \times 3$ ANOVA was performed with the within-subjects factors of Time (Pre and Post), Condition (Single Sham, Single Active, Repeated Active, Repeated Training Only), and Test (Invalid Left, Invalid Right, Phasic Alertness).

RESULTS

COMPUTERIZED MEASURES

At admission a complete hemianopia of the left visual field was diagnosed, which persisted until long-term follow up 3 months after the end of stimulation.

Intrinsic and phasic alertness were impaired at admission (intrinsic: $T = 40$; phasic: $T = 38$) with phasic alertness improving significantly after 1 week of standard therapy ($T = 45$, $p = 0.002$). After the single sham session combined with neglect therapy alertness worsened significantly (intrinsic: $T = 39$, $p < 0.001$; phasic: $T = 38$, $p < 0.001$), whereas after the single real session, alertness improved significantly (intrinsic: $T = 45$, $p = 0.008$; phasic: $T = 49$, $p < 0.001$). Both alertness parameters remained within normal levels after the first combined real tDCS treatment (**Tables 1**, **2**, **Figures 3E,F**).

Covert attention to *valid right-sided stimuli* was within normal performance levels throughout the study. *Covert attention to valid left-sided stimuli* was strongly impaired at admission, showed significant improvements during standard therapy also reaching a stable and normal level after the first combined real tDCS treatment, and was maintained until long-term follow-up (**Tables 1, 2**).

Covert attention to invalid right-sided stimuli fluctuated at training onset, but stayed below average levels before stimulation onset. After the first single real stimulation it also reached normal levels ($T = 50$). After the weekend on the first day of repeated stimulations RTs had declined again ($T = 34$), but again showed a significant improvement immediately after the first of the repeated stimulation sessions ($T = 50$, $p < 0.001$), remained within normal levels during repeated stimulation sessions ($T = 44$, $p < 0.001$), further improved after the end of stimulation until follow-up 1 ($T = 53$, $p < 0.001$), and returned to post-stimulation levels until the long-term follow-up ($T = 42$, $p = 0.232$) (**Tables 1**, **2**, **Figure 3**).

Invalid left-sided stimuli were not perceived at baseline. By the beginning of week 2 the patient was able to perceive them, however, he showed no improvement after single sham stimulation ($T < 20$, no p-value), while significant improvements were observed after a single real stimulation ($T = 28$, $p = 0.025$). Similar as for invalid right-sided stimuli this improvement was not maintained, however, performance improved again even further after the first stimulation session of repeated stimulations ($T = 43$, $p < 0.001$) and remained significantly improved after repeated stimulations ($T = 31$, $p = 0.002$). During the 1-week follow-up with standard therapy performance remained within post-stimulation levels ($T = 29$, $p = 0.576$) and was maintained until long-term follow-up ($T = 31$, $p = 1.000$) (**Tables 1**, **2**, **Figure 3**).

The main interaction of Time, Condition, and Test was highly significant [$F_{(12,\ 456)} = 19.51$, $p < 0.001$, $\eta_p^2 = 0.34$]. This interaction was due to a significant interaction for Time and Condition for RTs for left invalid stimuli [$F_{(1,\ 80)} = 7.42$, $p < 0.001$, $\eta_p^2 = 0.22$], but not for right invalid stimuli [$F_{(3,\ 64)} = 0.50$, $p = 0.687$, $\eta_p^2 = 0.23$], or phasic alertness [$F_{(3,\ 312)} = 2.00$, $p = 0.113$, $\eta_p^2 = 0.02$]. The significant interaction for left invalid stimuli was partly explained by a strong trend of the single active condition leading to a larger improvement than the single sham condition [$F_{(1,\ 40)} = 4.00$, $p = 0.052$, $\eta_p^2 = 0.09$], but was mainly explained by a significantly larger improvement after repeated combined

Table 1 | Raw data alertness and covert attention.

Test	Pre (5) BL	Post (5) BL	Pre (1) sham	Post (1) sham	Pre (1) real	Post (1) real	Pre (5) real	Post (5) real	FU 11 week	FU 23 mo
Intrinsic alertness	309 ± 64	317 ± 89	276 ± 45	316 ± 51	311 ± 86	287 ± 64	249 ± 54	289 ± 80	299 ± 71	267 ± 46
Phasic alertness	301 ± 43	268 ± 64	262 ± 42	302 ± 72	301 ± 55	247 ± 44	232 ± 44	217 ± 47	214 ± 35	258 ± 38
Covert attention valid left	1859 ± 606	1083 ± 493	682 ± 239	413 ± 192	444 ± 213	347 ± 162	378 ± 221	343 ± 150	350 ± 158	350 ± 145
Covert attention valid right	403 ± 135	351 ± 71	316 ± 166	282 ± 66	321 ± 109	304 ± 90	299 ± 98	329 ± 81	298 ± 93	372 ± 71
Covert attention invalid left	–	–	1184 ± 652	874 ± 735	1310 ± 292	686 ± 365	1346 ± 364	650 ± 329	675 ± 368	569 ± 138
Covert attention invalid right	500 ± 174	764 ± 148	495 ± 149	495 ± 83	484 ± 98	446 ± 69	553 ± 70	472 ± 74	425 ± 40	488 ± 39

Abbreviations: BL, baseline standard therapy; (1): 1 therapy session; (5): 5 therapy sessions; FU 1: Follow-up 1 week after the end of stimulation (5 days of standard therapy); FU 2, Follow-up 3 months after the end of stimulation; Mo, months. –: Patient was not able to perceive stimuli. Shading indicates time-periods of combined real tDCS and standard therapy (light gray: single real stimulation; dark gray: repeated real stimulation). Values are presented as median reaction time ± standard deviation.

Table 2 | *T*- and *p*-values alertness and covert attention.

Test	Pre (5) BL	Post (5) BL	*p*-value	Pre (1) sham	Post (1) sham	*p*-value	Pre (1) real	Post (1) real	*p*-value	Pre (5) real	Post (5) real	*p*-value	FU 1 1 week	*p*-value	FU 2 3 mo	*p*-value
Intrinsic alertness	40 (42)	39 (36)	0.598	**48 (50)**	39 **(49)**	<0.001	40 (36)	**45** (42)	**0.008**	**51 (47)**	**45** (38)	0.002	**43** (40)	0.292	**51 (51)**	**0.002**
Phasic alertness	38 (51)	**45 (44)**	**0.002**	**46 (52)**	38 (42)	<0.001	38 **(48)**	**49 (51)**	**<0.001**	**50 (51)**	**56 (49)**	**0.009**	**57 (57)**	0.661	**46 (54)**	<0.001
Posner valid left	<20 (<20)	<20 (<20)	–	<20 (21)	**46** (25)	**<0.001***	40 (23)	**54** (26)	**<0.001**	**52** (23)	**54** (32)	0.264	**50** (27)	0.025	**50** (26)	0.025
Posner valid right	**45** (35)	**51 (51)**	0.099	**56** (32)	**66 (51)**	**0.006**	**55** (39)	**59** (42)	0.271	**61** (40)	**54 (46)**	0.054	**61** (41)	0.054	**51 (45)**	0.409
Posner invalid left	–	–	–	<20 (24)	<20 (24)	–	<20 (26)	28 (26)	**0.025***	<20 (26)	31 (26)	**0.002***	29 (26)	0.576	31 (33)	1.000
Posner invalid right	40 (28)	24 (30)	<0.001	40 (30)	40 (40)	1.000	42 (37)	**50 (45)**	**<0.001**	34 **(45)**	**44** (43)	**<0.001**	**53 (58)**	**0.000**	42 **(59)**	0.232

Abbreviations: BL, baseline standard therapy; (1): 1 therapy session; (5): 5 daily therapy sessions; FU 1, Follow-up 1 week after the end of stimulation (5 days of standard therapy); FU 2, Follow-up 3 months after the end of stimulation; Mo, months. –: Patient was not able to perceive stimuli and/or p-values could not be calculated (T < 20). Shading indicates time-periods of combined real tDCS and standard therapy (light gray: single real stimulation; dark gray: repeated real stimulation). T-values of median reaction time and of standard deviations are presented. P-values are two-sided. Bold font indicates performance levels within normal range of the norm population (T-values) or significant improvements (p-values).

**For T < 20 p-values were calculated using T = 20, significance of p-values for these time-points are therefore underestimated.*

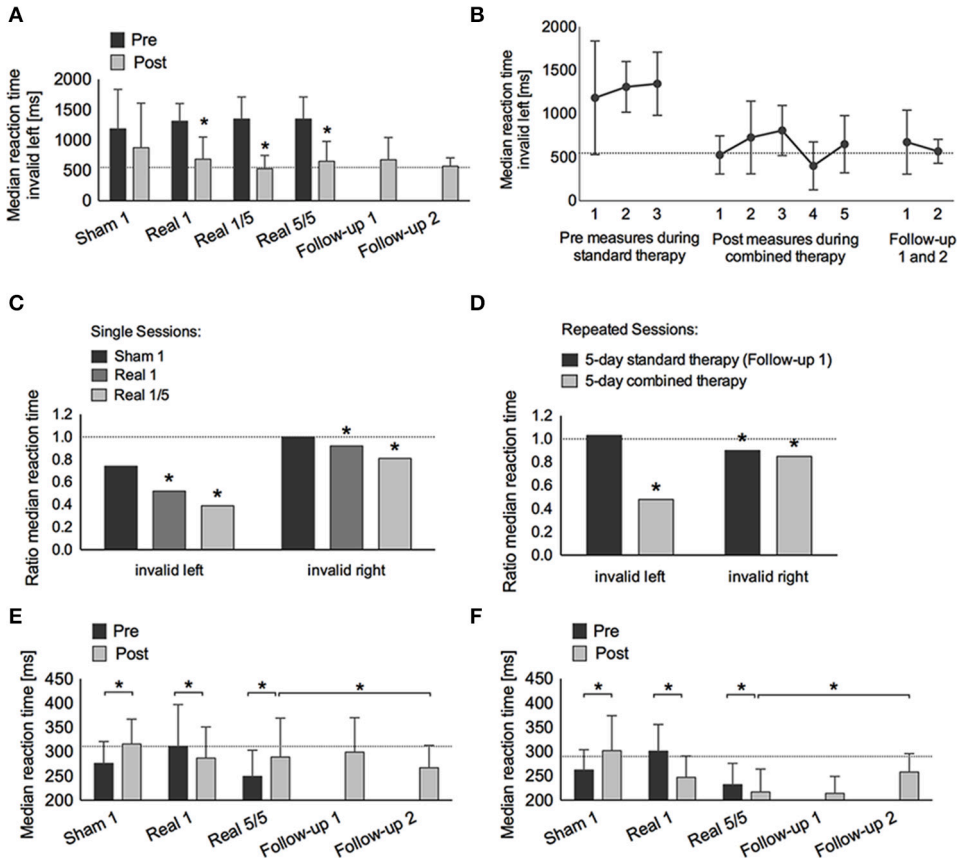

FIGURE 3 | Covert attention task (Posner paradigm, A–D) and alertness (E,F). (A) Median reaction time (±*SD*) to invalid left-sided stimuli pre (dark gray bars) and post (light gray bars) treatment: single-sham (Sham 1), single-real (Real 1), single-real on the first day of repetitive stimulation (Real 1/5), repeated-real during 5 days (Real 5/5), standard therapy during 1 week after the end of stimulation (Follow-up 1), and 3 months after the end of stimulation (Follow-up 2). **(B)** Median reaction time (±*SD*) to invalid left-sided stimuli on three different days before real stimulation (pre-measures), after five consecutive sessions with real stimulation (post-measures), and at Follow-up 1 and 2. **(C)** Ratio of median reaction time post-pre to invalid left- and right-sided stimuli after single-sham (Sham 1), single-real (Real 1), single-real on the first day of repetitive stimulation (Real 1/5), and **(D)** after repeated-real during 5 days, and standard therapy during 1 week after the end of stimulation (Follow-up 1). **(E,F)** Median reaction time (±*SD*) in intrinsic **(E)** and phasic **(F)** alertness. *at least $p < 0.05$.

treatment as compared to cognitive training alone [$F_{(1,\,40)} = 21.12$, $p < 0.001$, $\eta_p^2 = 0.35$].

PAPER-PENCIL MEASURES

Star cancelation performance fluctuated over the course of rehabilitation and did not vary with stimulation. However, both line bisection and figure copying improved after real stimulation sessions.

Line bisection was deviated toward the right after the single real stimulation session (5.3 ± 1.5 cm) and before beginning repeated stimulation (4.7 ± 1.4 cm). By the end of the stimulation-week the bisection had deviated toward the left side (−2.5 ± 1.7 cm) and was maintained over 3 days without stimulation (−1.8 ± 1.6 cm). However, by the end of the 1-week follow-up it returned to a rightward deviation (3.9 ± 0.7 cm), but reimproved until the long-term follow-up (0.9 ± 2.3 cm) (**Figure 4**).

Figure copying was clearly impaired at baseline (5/9 points). After the single real stimulation it improved by 1 point (6/9 points) and improved another 2 points (8/9 points) after repeated stimulation sessions. However, performance declined again after the end of real stimulation (6/9 points both at the 1-week as well as the 3-month follow-up) (**Figure 5**).

ACTIVITIES OF DAILY LIVING

During his stay at the rehabilitation center, N.H. did not show an improvement in ADL as measured with the BRS (Baseline: 0.9 points; after repeated stimulations: 1.22 points). Only at the 3-month follow-up all parameters showed an improvement (0.16 points).

SIDE-EFFECTS

The patient reported tingling sensations after the single sham as well as after each of the real stimulation sessions.

DISCUSSION

This single-case study investigated the long-term impact of repetitive, biparietal tDCS on neglect symptoms in subacute stroke. We found a significantly larger improvement in therapy outcome

after combined biparietal tDCS and cognitive training, while cognitive training on its own after single treatment sessions as well as repeated sessions over a time-period of 5 days did not lead to significant changes. Improvements in covert attention as well as alertness were maintained over a follow-up period of 1 week as well as a follow-up period of 3 months after the end of stimulation, whereas performance improvements in paper-pencil tasks were transient, returning to pre-stimulation levels at follow-up.

The main outcome measure (covert attention to left-sided stimuli according to the Posner paradigm) showed the strongest improvement, which was maintained until long-term follow-up, however, without reaching normal levels. Though RTs to invalid stimuli presented in the right hemi-field were also significantly modulated by stimulation, the effects were not as strong as for RTs to left-sided invalid stimuli. When comparing stimulation effects on RTs toward left and right invalid stimuli as well as alertness over the different stimulation conditions (single/repeated, with/without tDCS), only RTs toward left invalid stimuli were significantly modulated by stimulation. This finding supports the assumption of an asymmetrical distribution of brain activity in spatial attention, where the right hemisphere is dominant for orientation of covert attention to either hemi-field (Heilman and Van Den Abell, 1980; Corbetta et al., 1993). On the other hand it corroborates the hypothesis that reducing over-excitability in the undamaged hemisphere can have a beneficial impact.

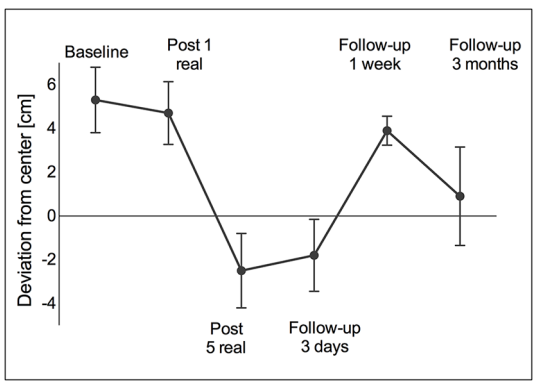

FIGURE 4 | Line bisection. A right-sided deviation was observed at baseline and remained right-sided after one real stimulation session. However, after five daily stimulation sessions the deviation turned to the left (over-compensation) and remained left-sided for another 3 days of standard therapy. At the 1-week follow-up as well as at the 3-month follow-up the deviation returned to the right again. Values are presented as mean ± standard deviation (SD).

Alertness measures were used as control measures. After one session of sham tDCS combined with neglect therapy intrinsic and phasic alertness were reduced, which could be due to fatigue. However, after one session of real tDCS, alertness improved significantly. Right frontoparietal areas are specifically important for alertness functions, which might explain why the placement of the anode over the right parietal cortex showed a beneficial impact. Nevertheless, alertness was not the driving factor for the improvement in the RTs toward left-invalid stimuli as we could show that after this initial improvement alertness measures remained within an age-matched norm level and did not show the same pattern of change as RTs toward left-invalid stimuli.

Interestingly, an improvement in most cognitive measures was observed after only one real stimulation session. However, further improvement and stabilization might arise only during repeated and specific combined treatment, which might trigger physiological processes that promote ongoing spontaneous recovery processes. Previous studies found significant long-term changes after only one tDCS session (e.g., Flöel et al., 2012). Effects of tDCS have been associated with NMDA-receptor dependent changes that reflect processes of long-term potentiation (LTP) and depression (LTD) that can become apparent even during or immediately after non-invasive brain stimulation (Liebetanz et al., 2002; Nitsche et al., 2003).

Qualitative performance in the cancelation task was not modulated by stimulation, while performance in figure copying as well as line bisection showed a maximal increase after 5 days of repeated stimulation. In the line bisection task an initially strong ipsilesional deviation, which can be typically observed in neglect patients, turned into a contralesional deviation after repeated tDCS sessions. Such a pattern can be interpreted as over-compensation and occurs usually in patients with hemianopia. Interestingly, over-compensation could still be observed 3 days

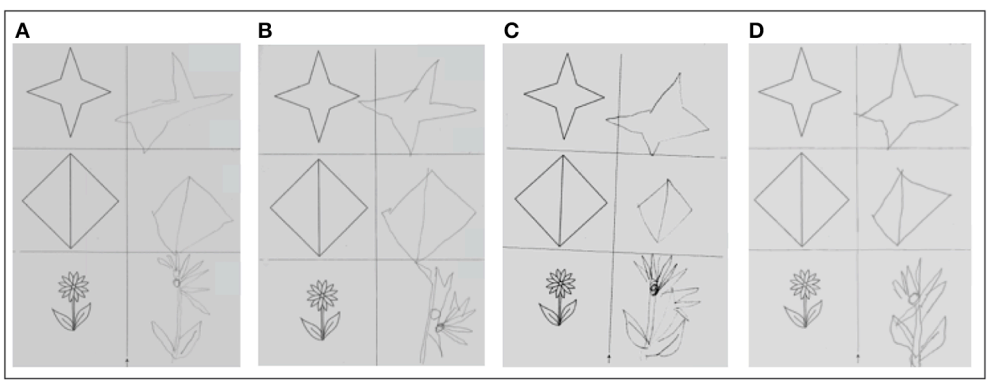

FIGURE 5 | Figure copying. (A) Before single real stimulation (5/9 points); **(B)** after single real stimulation (6/9 points); **(C)** before 5 daily real stimulations (6/9 points); **(D)** after 5 daily real stimulations (8/9 points).

after the end of stimulation but returned to an ipsilesional deviation at the 1-week follow-up, and finally approached normal levels at the 3-month follow-up. Sparing et al. (2009) also observed a reduction of deviation in a line bisection task but no over-compensation. This effect may be related to the bilateral approach used in the present study. In sum, improvements in paper-pencil tasks were not maintained until the 1-week and 3-month follow-up.

During the rehabilitation period, no measurable transfer of positive effects on ADL was observed. Improvements were only noticeable at the 3-month follow-up. Therefore, it is not possible to determine the association of changes in ADL with stimulation effects. However, in a study by Shindo et al. (2006) most improvement occurred 2–4 weeks after repeated rTMS sessions, which supports the assumption of a kick-off effect of stimulation, which may only later translate into ADL improvements.

It remains to be confirmed in future studies in larger patient samples and including a longer follow-up period that repeated sessions may not only result in a long-term improvement but also have a positive transfer effect on ADL functions. Additional assessments of physiological correlates could furthermore help to elucidate possible delayed stimulation effects.

Several drawbacks of this study need to be mentioned, which are mostly due to the fact that the investigation took place during the subacute stage. First, spontaneous recovery processes need to be taken into account (Cramer, 2008). Furthermore, we cannot rule out the possibility that effects are due to cognitive training alone. Second, the patient participated in other neurorehabilitative programs and practiced by himself. Both of these factors could explain the observed improvements. However, specific effects during the active and sham single sessions contradict these explanations. Furthermore, we would expect continuous improvement over time. Third, some of the paper-pencil tasks could not be assessed at all test-times due to fatigue and time restrictions. Fourth, one could argue that positive effects were caused by a mere improvement of alertness. Though alertness functions might modulate neglect symptoms (Sturm et al., 2006), they do not alone account for this improvement (e.g., after sham stimulation we observe opposite effects on alertness and covert attention). Furthermore, while alertness remained variable within normal levels during repeated stimulation, RTs to invalid stimuli in the covert attention measure improved further. Nyffeler et al. (2009) also suggested that effects were not due to an unspecific increase of alertness, as RTs to right-sided stimuli did not change significantly in their study. We found neither a significant modulating effect of stimulation for alertness nor for invalid right-sided stimuli. Finally, it is in the nature of single-case studies that it is not possible to generalize results to a greater population. Nevertheless, they are helpful in guiding future studies with larger patient populations and can give us valuable insight into specific diseases, providing unique information that might be useful for individualized treatment approaches. Specifically in the subacute stage after a stroke many factors contribute to a large variability, which is a reason why few studies investigate the impact of brain stimulation in subacute patients, although this might be the most fruitful period to stimulate the brain. We may be able to support and guide ongoing compensatory and restitution processes not only through behavioral therapies, but combine them with non-invasive brain stimulation in order to increase beneficial effects.

In sum, during combined therapy functional improvement was significantly higher than during standard therapy alone and was maintained over a follow-up period of 1 week and 3 months. A transfer effect to ADL was only observed at the long-term follow up. Future studies should investigate larger patient populations and longer treatments periods.

AUTHOR CONTRIBUTIONS

Anna-Katharine Brem and Lutz Jäncke designed the study. Anna-Katharine Brem, Evelyn Unterburger, and Irving Speight contributed to data collection and analysis. Anna-Katharine Brem prepared the draft report, which was critically reviewed by all authors.

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REVIEW
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Modulating pathological oscillations by rhythmic non-invasive brain stimulation—a therapeutic concept?

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A large amount of studies of the last decades revealed an association between human behavior and oscillatory activity in the human brain. Alike, abnormalities of oscillatory activity were related with pathological behavior in many neuropsychiatric disorders, such as in Parkinson's disease (PD) or in schizophrenia (SCZ). As a therapeutic tool, non-invasive brain stimulation (NIBS) has demonstrated the potential to improve behavioral performance in patients suffering from neuropsychiatric disorders. Since evidence accumulates that NIBS might be able to modulate oscillatory activity and related behavior in a scientific setting, this review focuses on discussing potential interventional strategies to target abnormalities in oscillatory activity in neuropsychiatric disorders. In particular, we will review oscillatory changes described in patients after stroke, with PD or suffering from SCZ. Potential ways of targeting interventionally the underlying pathological oscillations to improve related pathological behavior will be further discussed.

Keywords: non-invasive brain stimulation, oscillatory activity, stroke, Parkinson's disease, schizophrenia

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Importance of Oscillations for Information Processing in the Healthy Brain

Since Berger first described oscillatory activity of the brain in the 1920s, oscillations have been investigated extensively and research revealed clear relevance of human brain oscillations for information processing and behavior (Singer and Gray, 1995; Engel et al., 2001; Brown, 2003; Buzsáki and Draguhn, 2004; Pfurtscheller et al., 2005; Schoffelen et al., 2005; Fries, 2009; Jensen and Mazaheri, 2010).

Generally, an oscillation is a periodic fluctuation caused by changes in excitability of a group of neurons, measured on the scalp as differences in voltage with techniques like electroencephalography (EEG) or magnetencephalography (MEG). Oscillations are suggested to be able to temporally coordinate and control neuronal firing and are proposed to be one basic principle of information processing in the human brain (Engel et al., 2001; Varela et al., 2001; Buzsáki and Draguhn, 2004). Based on phenomenological observations, a division in frequency bands has been established. Usually, oscillation frequencies are categorized as delta-band (1.5–4 Hz), theta-band (4–7 Hz), alpha-band (8–12 Hz), beta-band (12–30 Hz) and gamma-band (30–80 Hz). Since this review will focus on specific aspects of pathological oscillatory activity, the next paragraph will briefly introduce selected relevant findings for each frequency band in the healthy brain.

Slow delta-band resting-state oscillations are prominent in sleep and are, like theta-band oscillations, associated with memory consolidation (Marshall et al., 2006; Rasch and Born, 2013). Alpha-band oscillations are prominent oscillations in the resting brain and alpha-band activity is associated with a wide range of brain functions like visual perception (Busch et al., 2009), working memory and short-term-memory retention (Palva and Palva, 2007). Alpha-band responses to eyes closing and opening respectively have been described since the first EEG-recordings and have been interpreted as desynchronization of affected neurons by information processing. This task-related suppression of alpha-band activity has been extensively investigated for other areas like motor cortex, and is called event-related desynchronization (Pfurtscheller, 1992; Klimesch et al., 2007). Besides event-related desynchronisation, there is event-related synchronization, which has been proposed to reflect cortical idling (Pfurtscheller et al., 1996). Furthermore, alpha-band activity was induced during inhibitory control processes (Hummel et al., 2002; Haegens et al., 2010; Jensen and Mazaheri, 2010; Sauseng et al., 2013). Beta-band oscillations are, like alpha-band oscillations, involved in perceptual processes (Engel and Fries, 2010). Another functional relevance of beta-band oscillations is sensorimotor control, their activity has been described during motor tasks and maintenance of contractions (Pfurtscheller and Lopes da Silva, 1999; Kilner et al., 2000; Engel and Fries, 2010). Since beta oscillations are described to be associated with a steady state of the motor system, it has been hypothesized that they signal the "status quo" (Gilbertson et al., 2005; Engel and Fries, 2010). Having been extensively investigated, task-related or evoked gamma-band oscillations respectively are thought to be involved into a broad range of behavioral components like visual perception and attention, and are associated with several memory functions (Singer and Gray, 1995; Tallon-Baudry et al., 1998; Herrmann et al., 2004; Jensen et al., 2007).

Moreover, besides local phenomena, mechanisms of oscillatory communication have been identified. For example synchronization of phases is suggested to be one basic principle for long range communication and is a component of connectivity measurements like coherence (Varela et al., 2001; Hummel and Gerloff, 2005; Schoffelen et al., 2005). Furthermore high frequency activity has been described as being depended on low frequency phase (Osipova et al., 2008; Jensen and Mazaheri, 2010; Buzsáki and Wang, 2012).

Underlining a potential causal relationship, both oscillatory activity and behavior were modulated by non-invasive brain stimulation (NIBS) in several studies. Before focussing on abnormal oscillations and pathological behavior, the influence of NIBS on oscillations of the healthy brain will be discussed in the next section.

Modulation of Oscillations by Rhythmic NIBS in the Healthy Brain

Several recent studies combining NIBS and EEG revealed that NIBS is able to modulate oscillations in the healthy brain (Plewnia et al., 2008; Pogosyan et al., 2009; Zaehle et al., 2010; Thut et al., 2011; Vernet et al., 2013). Generally, one basic technique of NIBS is Transcranial Magnetic Stimulation (TMS). By depolarization of neurons, a TMS single pulse applied over the hand knob area typically leads to a motor evoked potential in the contralateral hand (Hummel and Cohen, 2005; Hallett, 2007). Combining TMS with EEG, an increase of the intrinsic frequency of the TMS-affected area and their thalamic loops respectively has been observed (Rosanova et al., 2009). Another basic method of NIBS is Transcranial Electric Stimulation (TES). In contrast to TMS, TES is suggested to tune oscillators by modulating the membrane potential of neurons and their spontaneous firing rates (Nitsche and Paulus, 2000).

Regarding rhythmic applications of TMS, there is e.g., the theta burst stimulation (TBS) protocol, in which a triple pulse with an interpulse frequency of 50 Hz is applied in a theta rhythm. Applied continuously, TBS has an inhibitory effect, applied in an intermittent mode TBS has an excitatory effect (Huang et al., 2005; Hallett, 2007). Furthermore, repetitive TMS (rTMS) applied in a frequency below or at 1 Hz has an inhibitory effect, application of frequencies at faster rates (>5 Hz) leads to excitation (Pascual-Leone et al., 1994; Hummel and Cohen, 2005). Regarding patterned applications of TES, there is transcranial alternating current stimulation (tACS), a sinusoidal stimulation with spatially alternating anodal and cathodal components. Furthermore, there are transcranial random noise stimulation (tRNS) and direct current stimulation with a sinusoidal component, called oscillatory tDCS (Siebner and Ziemann, 2010).

Depending on their effect on oscillations, a division of rhythmic applications of NIBS into two concepts has been proposed (Siebner and Ziemann, 2010). On the one hand rhythmic NIBS can be applied in an oscillatory mode in the frequency of the targeted oscillation or its oscillator, respectively (Pogosyan et al., 2009; Zaehle et al., 2010; Thut et al., 2011). In the following, this mode will be called "direct", because there is a direct interference of stimulation frequency and the frequency of the oscillator. On the other hand, one can apply rhythmic NIBS in a non oscillatory mode, not reflecting the targeted oscillations or the frequency of the targeted oscillator. In this case NIBS is suggested to modulate underlying oscillatory mechanisms (Nitsche and Paulus, 2000; Lapenta et al., 2013; Vernet et al., 2013). This non oscillatory mode will be called "indirect" in the following.

In a study on "direct" modulation of ongoing oscillations, five pulses of TMS with an adjusted individual alpha frequency were able to entrain a parietal alpha oscillator specifically in its natural frequency (Thut et al., 2011). tACS entrained individual parietal-central alpha oscillations if applied in the endogenous frequency at the occipital pole (Zaehle et al., 2010). Furthermore, 10 Hz repetitive bifocal TMS over left primary motor cortex and over visual cortex led to an increase of alpha-band and lower beta coherence between the stimulated sites (Plewnia et al., 2008), supporting the

exciting concept to not only influence local oscillatory activity but also long-range oscillatory interactions by NIBS.

Combining NIBS with EEG, "direct" applications of NIBS also modulated both oscillatory activity and behavioral components, thereby providing evidence for a causal role of oscillations and its modulation. In a visuomotor task tACS applied at 20 Hz reduced peak velocity on the one hand and increased coherence between scalp-recorded activity and EMG activity at 20 Hz on the other hand (Pogosyan et al., 2009). Recently it has been shown by concurrent EEG-tACS that 10 Hz stimulation can entrain parieto-occipital alpha activity and modulate target detection performance in an oddball task in a phase-dependent manner (Helfrich et al., 2014). In an auditory experiment perception thresholds were dependent on the phase of the entrained oscillation using 10 Hz oscillatory tDCS (Neuling et al., 2012). Furthermore slow wave oscillatory tDCS in a frequency of 0.75 Hz applied during non-rapid-eye-movement sleep induced an increase of slow wave oscillations and enhanced the retention of declarative memories (Marshall et al., 2006). However, this study was critically evaluated by the same group showing that the total amount of current and not the oscillatory component of the oscillatory tDCS might have been the main effective variable (Groppa et al., 2010).

As an "indirect" rhythmic application of NIBS, continuous theta burst stimulation (cTBS) increased theta-band power and decreased beta-band power in an eyes-closed resting experiment (Vernet et al., 2013). As an underlying mechanism the authors suggest that cTBS modulates synchronization of relevant oscillators. In a non resting setup cTBS increased event-related lower beta power applied over primary motor cortex for at least 30 min (Noh et al., 2012) and 40 trains of ten excitatory TMS pulses at 20 Hz increased alpha and beta-band event-related synchronization at the stimulation site (Veniero et al., 2011).

Like "direct" applications, also "indirect" applications were able to modulate both oscillations and behavior. Inhibitory 1 Hz rTMS on right prefrontal cortex reduced both response times for congruent cued targets and ipsilateral alpha amplitude (Sauseng et al., 2011). In another study 5 Hz tDCS (theta tDCS) decreased both slow wave activity, frontal slow EEG spindle power and consolidation of declarative memory (Marshall et al., 2011).

Taken together evidence is increasing that oscillations, being one basic principle of information processing in the human brain, can be modulated by NIBS. In many cases, this suggests a possible mechanism for how NIBS may exert its effects on cognitive processes or behavior.

In the following paragraph, alteration of oscillatory activity will be discussed as a pathophysiological mechanism in neuropsychiatric disorders. As examples, we will consider oscillatory changes in the alpha-band after stroke, beta-band changes in patients with Parkinson's disease (PD) and altered gamma-band activity in patients suffering from schizophrenia (SCZ). Next, we will discuss potential applications of rhythmic NIBS like rTMS and tACS in order to modulate pathological oscillations and potentially improve the clinical outcome in patients.

Role of Oscillatory Activity in the Pathophysiology of Neuropsychiatric Disorders

Stroke is one of the leading causes for acquired long-term disability in industrialized countries (Kolominsky-Rabas et al., 2001) and, therefore, studies on neurophysiological changes accompanying and following stroke have received considerable interest.

Several studies have observed changes in alpha-band activity recorded over the affected hemisphere (AH) after stroke in the resting brain (Tecchio et al., 2005, 2006; Dubovik et al., 2012; Westlake et al., 2012; Laaksonen et al., 2013). Thirty-two patients with stroke of the middle cerebral artery within the first 10 days (Tecchio et al., 2005) and 56 stroke patients in a chronic stage (Tecchio et al., 2006) showed a reduction of the individual alpha frequency in the AH. In 16 patients with affected upper limp function, amplitude of alpha-band oscillations increased in the AH compared to the unaffected hemisphere (UH) and to control subjects 1 month and 3 months after stroke (Laaksonen et al., 2013). In the latter study, alpha oscillations had a burst-like pattern and were found both in rolandic and in parietal regions. However, these changes in alpha-band activity did not correlate with the clinical outcome in patients (Tecchio et al., 2005, 2006; Laaksonen et al., 2013).

In contrast, two studies addressing interregional resting-state functional connectivity (FC, based on imaginary coherence, IC) were able to correlate changes of alpha-band activity with performance (Dubovik et al., 2012) and motor recovery (Westlake et al., 2012) after stroke. Twenty patients showed a decrease of alpha-band FC of central electrodes over the lesions to all other electrodes 3 months after stroke of middle or/and anterior cerebral artery (Dubovik et al., 2012). Moreover, motor functions correlated with IC values of the precentral gyrus and all other investigated brain regions. Since FC changes were not restricted to the boundaries of the lesions but restricted to a specific frequency, the authors emphasize that oscillatory changes are probably not due to tissue loss but to changes in affected tissue. Furthermore the study showed that changes in FC are probably due to changes in alpha phase synchrony rather than to changes in alpha amplitude (Stam et al., 2007; Dubovik et al., 2012). Another study found changes in alpha-band activity in the acute phase of stroke (Westlake et al., 2012). Greater initial functional alpha-band connectivity of ipsilesional primary sensory cortex and prefrontal cortex in the acute phase correlated with better clinical improvement 8–12 weeks after stroke in fourteen patients with motor impairment of the upper limb.

Next to changes in alpha-band activity, also changes of slow wave oscillations were found after brain injuries like head trauma and stroke (Lewine et al., 1999; Butz et al., 2004). In line with these results a shift from fast to slow rhythms could be observed after stroke (Dubovik et al., 2012) and slow delta wave oscillations of the UH have been shown to be correlated with clinical outcome after stroke (Tecchio et al., 2007). Patients

with persisting abnormal slow wave oscillations (abnormal low frequency magnetic activity) had a significantly worse clinical outcome compared to patients without persisting slow wave oscillatory components (Laaksonen et al., 2013).

Besides clinical observations, slow wave activity has also been investigated in an animal stroke model, in which slow wave oscillations were associated with axonal sprouting after thermal-ischemic lesioning (Carmichael and Chesselet, 2002). In this model, a treatment with tetrodotoxin reduced both slow oscillations and axonal sprouting. In another study neuronal bursts were able to reduce inhibitory factors that surround axons (Ming et al., 2001). In a recent publication it could be shown that new patterns of axonal sprouting mediated recovery after stroke in an animal model (Overman et al., 2012). Taken together, these data provided first evidence that there might be an association of slow neuronal firing, axonal sprouting and behavioral recovery.

PD has a high prevalence in aging populations (von Campenhausen et al., 2005). Evidence is increasing that clinical symptoms of PD are related to abnormalities in beta-band activity (Levy et al., 2002; Kühn et al., 2008, 2009; Crowell et al., 2012; Heinrichs-Graham et al., 2014; Herz et al., 2014). Prominent beta-band activity has been recorded in the basal ganglia in animal models of PD and in PD patients with deep brain stimulation (DBS; Levy et al., 2000, 2002; Kühn et al., 2008; Bergmann et al., 2012; Heinrichs-Graham et al., 2014; Herz et al., 2014). Both dopamine treatment and DBS have been shown to reduce beta-band activity (Brown et al., 2001; Levy et al., 2002; Kühn et al., 2008). The modulation of beta-band activity by dopaminergic treatment (Kühn et al., 2009) and by DBS (Ray et al., 2008) was associated with a reduction of bradykinesia and rigidity. A recent study in PD also revealed that treatment with levodopa reinforced beta-band coupling between primary motor cortex and lateral premotor cortex (Herz et al., 2014). Another study demonstrated a lack of physiological event-related beta desynchronization which could be modulated by levodopa in PD (Heinrichs-Graham et al., 2014). Taken together, in PD abnormal beta oscillations are a consistent finding with a strong relation to abnormal behavior. Hence, beta-band oscillations could be a promising target for interventional strategies based on rhythmic NIBS.

SCZ has a life-time prevalence of 0.4% and belongs to the thirty most disabling disorders worldwide (Murray and Lopez, 1997; McGrath et al., 2008). Besides psychotic symptoms patients with SCZ show abnormalities in cognitive performance, e.g., in working memory, cognitive control and sensory gating. These cognitive deficits are, on the one hand, associated with clinical and functional outcome (Green et al., 2000; Gold, 2004; McGrath et al., 2008). On the other hand they are related with abnormalities in gamma-band oscillations (Johannesen et al., 2005; Uhlhaas et al., 2008; Barr et al., 2010; Sun et al., 2011). Compared to healthy controls, patients with SCZ showed excessive gamma-band oscillations in conditions with high memory load (Barr et al., 2010). Altered gamma-band activity was also found in the resting brain of SCZ patients (Andreou et al., 2014). Furthermore, evoked gamma power and phase synchronization were reduced after auditory stimulation in patients with SCZ (Light et al., 2006). In line with these results, after a 40 Hz binaural stimulation a reduced phase locking between primary auditory cortices was observed in patients with SCZ, which correlated with auditory hallucination scores (Mulert et al., 2011).

Moreover, combination of TMS and EEG has been used in SCZ research by using a TMS double pulse paradigm (Farzan et al., 2009) called long intracortical inhibition (LICI). LICI is an established, probably $GABA_B$ mediated measurement for cortical inhibition in motor cortex using motor-evoked potentials as a readout (McDonnell et al., 2006). Both $GABA_A$ and $GABA_B$ suggested to be involved in the generation of gamma-band oscillations (Wang and Buzsáki, 1996; Brown et al., 2007). Recently, EEG parameters were established as another readout for double pulse TMS paradigms in non motor areas like DLPFC (Daskalakis et al., 2008). A study in healthy subjects demonstrated that applying a TMS LICI protocol over DLPFC led to a decrease of gamma oscillations whereas gamma oscillations over motor cortex did not change after LICI application (Farzan et al., 2009). In contrast, patients with SCZ showed an impaired LICI-mediated inhibition of gamma oscillations in DLPFC compared to healthy participants and patients with bipolar disorder (Farzan et al., 2010a).

In summary, gamma-band oscillations have been related with cognitive performance in the healthy brain (Tallon-Baudry et al., 1998; Herrmann et al., 2004). In SCZ abnormal gamma-band activity was associated with behavioral impairment (Johannesen et al., 2005; Uhlhaas et al., 2008; Barr et al., 2010; Sun et al., 2011; Andreou et al., 2014). In line with these results, gamma-band activity could be one potential target of NIBS in SCZ.

Targeting Pathological Oscillations by Non-Invasive Brain Stimulation

This section will address the question of how rhythmic NIBS could be used to modulate pathological oscillations and thereby modulate behavior and clinical symptoms in stroke, PD and SCZ.

Several studies have demonstrated that NIBS can improve functional outcome of stroke patients (Hummel and Cohen, 2005; Hummel et al., 2005, 2006; Kim et al., 2006; Cazzoli et al., 2012; for review Schulz et al., 2013). To our knowledge, however, there is to date limited data on the effect of NIBS on oscillations in stroke. In six patients with severe hemiparesis, tDCS modulated alpha-band oscillations of sensorimotor areas during imaginary movements of the affected hand (Kasashima et al., 2012). Since detection of stable brain rhythms can be difficult in damaged brain areas after stroke, the aim of the latter study was to enhance oscillatory activity in the lesioned hemisphere by tDCS in order to be able to achieve a stable and well distinguishable brain signal for use in a brain-computer-interface (BCI). Event related alpha-band desynchronisation, a correlate of local activation, was significantly enhanced after tDCS stimulation compared to sham stimulation, making the signal more suitable for a BCI.

Although several studies have applied NIBS in stroke patients, only one case report has used rhythmic NIBS to modulate oscillations. In a patient with aphasia 10 Hz rTMS modulated both oscillatory activity and clinical outcome (Dammekens et al., 2014). In the treated patient the stroke lesion affected the left

inferior frontal gyrus (IFG), which is part of the language network (Crosson et al., 2007). Generally, according to the concept of an interhemispheric rivalry in stroke (Murase et al., 2004; Duque et al., 2005), inhibitory rTMS protocols of 1 Hz stimulation frequency are applied to the healthy hemisphere in order to prevent interhemispheric maladaptive processes in contralesional networks. Another approach is to excite the damaged hemisphere with rTMS protocols with a frequency above 5 Hz (Lefaucheur, 2006). In the latter study, excitatory rTMS was applied over the damaged left IFG in daily sessions over 3 weeks leading to an increase of FC between left and right IFG in the theta- and high beta-band. Behaviorally, the patient improved on repetition tasks for naming and comprehension. In addition to being a case report, this study does certainly not establish a causal relation between modulation of oscillations and changes in behavior. Nevertheless, this study provides first hints that rhythmic NIBS might be effective in modulating both oscillatory activity and clinical outcome.

Based on the emerging understanding about the relationship between NIBS and the modulation or induction of oscillatory activity in the last decad, hypotheses on how to enhance brain functioning and ameliorate impaired behavior after focal brain lesions can be defined. These hypotheses would be amenable to evaluation in controlled clinical trials in stroke patients. Combining the evidence that (1) changes in alpha-band activity are correlated with recovery and performance after stroke (Dubovik et al., 2012; Westlake et al., 2012) and that (2) NIBS is able modulate alpha-band activity (Plewnia et al., 2008; Thut et al., 2011) one could consider applying rhythmic alpha-NIBS after stroke. As illustrated schematically in **Figure 1A**, bifocal TMS at alpha frequency could entrain alpha-band activity between lesioned areas and relevant neighboring regions. In this context, bifocal application should potentially be performed with a certain phase lag between the targeted areas. An application of less focal alpha tACS in a montage covering both targeted areas would be another option. In both cases rhythmic NIBS would potentially lead to a synchronization in the alpha-band of lesioned sites and relevant connected areas like ipsilateral and contralateral premotor cortices respectively (Johansen-Berg et al., 2002; Ward et al., 2003; Gerloff et al., 2006; Rehme et al., 2011; Dubovik et al., 2012; Westlake et al., 2012).

Another option to entrain alpha-band activity could be to add noise, as shown in **Figure 1B**. tRNS is a technique which has been used to modulate cortical excitability and BOLD activity (Terney et al., 2008; Saiote et al., 2013). It has been suggested that, by adding noise, tRNS is able to augment cortical oscillations of different frequencies (Antal and Paulus, 2013). In stroke patients, tRNS could elevate reduced alpha-band activity in affected parts of the brain back to suprathreshold levels (Moss et al., 2004) and thereby restore important connective functions. Analogue to the potential effects on the aging brain, rhythmic or patterned NIBS like tRNS, tACS and rTMS could be used to entrain recruitment of other brain areas to support both affected networks and functional outcome (Gutchess, 2014).

Regarding the results of reduced alpha peak frequency and increased alpha amplitude in the AH after stroke (Tecchio et al., 2005) one could argue that behavioral changes might be related to alpha induced inhibition (Jensen and Mazaheri, 2010). In contrast to changes in FC (Dubovik et al., 2012; Westlake et al., 2012), these changes were not correlated with behavioral changes, however, and gaining clinical benefit by modulating these features of local oscillatory activity remains an untested possibility.

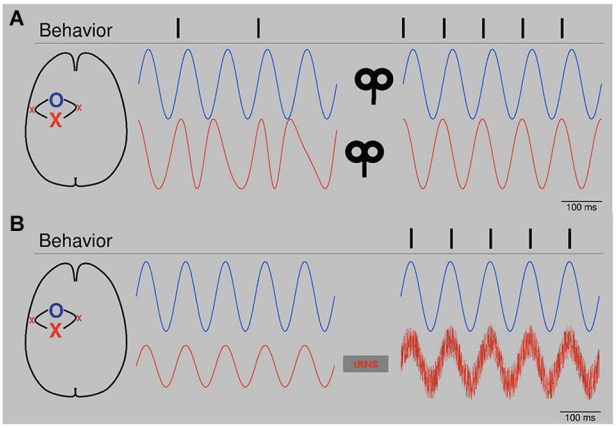

FIGURE 1 | (A) Schematic: Bifocal repetitive TMS (rTMS) restores alpha-band activity. After stroke, alpha oscillators (red line, left) of the affected area (red X, primary motor cortex) show unsteady phase properties. Since physiological behavior depends on a constant phase relation of alpha oscillations between the affected area and connected networks (blue O, blue line, left, premotor areas), the patient is impaired (behavior, left, e.g., muscle contractions). After application of bifocal, rTMS at alpha frequency over both areas with a lag reflecting physiological offset of oscillators, oscillatory activity is synchronized (blue and red line, right) in terms of a constant phase lag. Behavior improves (right). Please note that conditions are highly simplified. First, next to phase, also amplitude is important for signal processing. Second, in the presented physiological condition (right) phases are completely locked, which is artificial. Naturally, phases would fluctuate. **(B)** Schematic: tRNS augments alpha oscillators. After stroke alpha activity (red line, left) of the affected area (red X) is reduced. Threshold for establishing information processing with a related network (blue line, left) is not reached and dependent normal behavior is reduced. tRNS applied over the affected oscillator augments alpha activity by adding noise (red line, right). Information processing is re-established and behavior improves. Please note that conditions are very much simplified. In both cases, phase is totally locked without any phase lag. Biological signals would fluctuate.

In addition to the modulation of electrophysiological dynamics, NIBS might also influence molecular environment of neurons. By modulating slow wave activity occurring after stroke (Tecchio et al., 2005; Dubovik et al., 2012; Laaksonen et al., 2013) related neural repair might be modulated. Since there is first evidence in an animal model that there might be an association of slow neuronal firing, axonal recovery and recovery of function (Ming et al., 2001; Carmichael and Chesselet, 2002; Overman et al., 2012), one should consider a slow frequency stimulation as performed before in different contexts (Marshall et al., 2011) to gain axonal sprouting and improve clinical outcome after brain injury like stroke.

As discussed in the preceding section, pathological beta oscillations are a consistent finding in basal ganglia correlated with behavioral changes in PD patients (Levy et al., 2002; Kühn

et al., 2008, 2009; Crowell et al., 2012; Heinrichs-Graham et al., 2014; Herz et al., 2014). It is known that these abnormal beta-band oscillations can be modulated by established DBS protocols. In addition, a number of studies investigated the effects of NIBS on motor function in patients with PD. Applying 5 Hz rTMS over primary motor cortex led to a short term increase of motor function in six PD patients (Siebner et al., 2000). A 5 Hz rTMS protocol consisting of 2000 pulses per day over ten days led to significant reduction of motor impairment (Khedr et al., 2003). Moreover, rTMS over inferior frontal cortex modulated event-related potentials in the subthalamic nucleus (STN) in patients with implanted DBS electrodes (Rektor et al., 2010). Though different stimulation locations were used for both techniques, resting-state functional-connectivity MRI analysis revealed, that targets of stimulation might be nodes in the same network (Fox et al., 2014).

In our view, the clinical effectiveness of these two stimulation techniques and their probably network-associated ability to modulate cortex-basal ganglia dynamics point to the great potential of NIBS applications in PD. As discussed above, pathological beta oscillations could be a promising target for rhythmic NIBS. A recent study has demonstrated the possibility to enhance the "akinetic" effect of beta oscillations. In a task where subjects got a cue to stop a planned grip-movement, tACS stimulation with 20 Hz significantly reduced grip force in that condition (Joundi et al., 2012). One the one hand these results underline the potential impact of enhanced beta oscillations in "akinetic" disorders like PD. On the other hand, the results point out the ability of cortical NIBS to affect loops involving the basal ganglia.

To our knowledge, however, it has not been possible to reduce pathological beta oscillations in PD by NIBS. Potentially, reducing beta activity could be achieved by phase cancellation. Phase cancellation by application of tACS has already been used for tremor reduction in PD. Targeting tremor-associated oscillations in such an approach in patients with tremor-dominant PD led to an almost 50% suppression of resting tremor (Brittain et al., 2013). As a first step in the study, the individual tremor frequency of each patient was measured. In a second step, tremor-frequency adjusted tACS was applied over the primary motor cortex at different phase angles. Certain phase angles led to tremor reduction whereas stimulation at different angles led to an increase of tremor. This study underlines the great potential of individualized application of rhythmic NIBS and suggests the potential efficacy of phase cancellation. Based on monkey data, phase cancellation has also been suggested as a physiological mechanism for controlling tremor in spinal cord networks (Williams et al., 2010). As illustrated schematically in **Figure 2A**, phase cancellation might be applied to pathological beta oscillations in PD potentially targeting bradykinesia and rigidity (Ray et al., 2008; Kühn et al., 2009).

Since tremor shifted to a different frequency in some of the patients in the study by Brittain et al. (2013), tACS application should be adjusted to ongoing tremor activity to provide an effective modulation, as shown schematically in **Figure 2B**. To this end, online read-out techniques that allow stimulation in dependence on ongoing oscillatory activity (Berényi et al., 2012; Bergmann et al., 2012) will be highly advantageous in order to adjust NIBS to changing pathologic frequency and provide effective phase cancellation and reduction of symptoms. In a clinical setting such an "online", closed-loop approach has already been tested successfully: in PD DBS has been triggered based on recorded local field potentials (Little et al., 2013). These interventional strategies are interesting and potentially promising for amelioration of symptoms not well responsive to DBS.

In SCZ, combining single or double pulse TMS with EEG revealed abnormalities of cortical inhibition of gamma oscillations (Farzan et al., 2009, 2010b). Both studies point towards a scientific benefit of combining these methods and suggest that measurements on TMS-evoked oscillatory activity could be useful as a "biomarker" for neuropsychiatric disorders. Applying a similar approach, TMS evoked EEG activity has been proposed to add information to diagnostic procedures for chronic disorders of consciousness (Ragazzoni et al., 2013).

Abnormal gamma-band oscillations of patients with SCZ have been modulated by rTMS (Barr et al., 2011). In an N-back working memory task, subjects were asked to compare stimuli with those from previous trials. 20 Hz TMS applied bilaterally to DLPFC in reduced gamma activity in the SCZ patients (Barr et al., 2011). This approach, which is schematically presented in **Figure 2C**, could be considered as an "indirect" application, in which underlying gamma oscillators were modulated by an excitatory 20 Hz rTMS protocol not directly targeted at gamma frequencies. Since rTMS of a single session in the latter study did not change working memory behavior, the same group performed a pilot study with 20 Hz rTMS over DLPFC bilateraly for twenty sessions in a randomized double-blinded sham-controlled manner. This application led to a significant improvement of accuracy in working memory underlining that rTMS might potentially improve cognitive impairments in SCZ patients (Barr et al., 2013). Moreover, these results point towards the need for repetitive sessions of NIBS to gain long term effects. However, changes in gamma oscillations were not addressed in this follow-up study (Barr et al., 2013).

Taken together, application of rTMS seem to be promising for the treatment of negative symptoms of SCZ, although so far only demonstrated in proof-of-principle studies. Gamma oscillations show a high diversity in SCZ (Sun et al., 2011) and, hence, a direct link between the modulation of gamma oscillations and an improved cognitive performance in SCZ remains speculative. Nevertheless, further applications for the treatment of negative symptoms based on safe and low cost NIBS techniques addressing specifically gamma oscillations should be further developed and evaluated in detail in future studies.

Summary and Further Perspectives of NIBS

Evidence is increasing that NIBS may provide a novel and promising strategy to modulate both oscillatory activity and related behavior in the healthy brain. To date only a limited number of studies have employed NIBS to modulate oscillatory

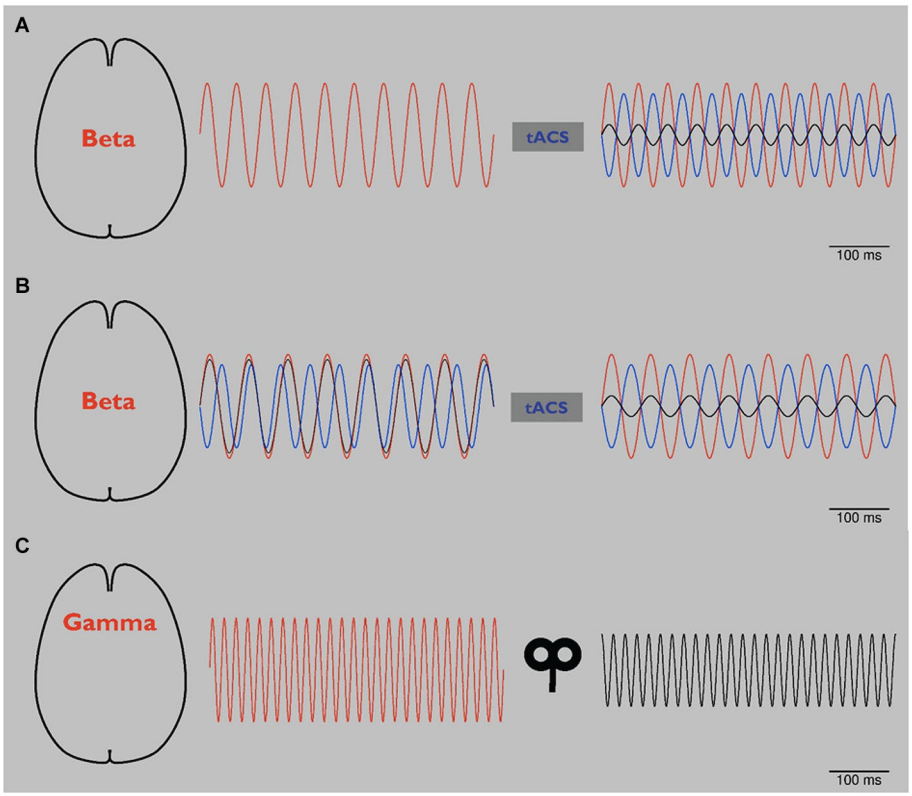

FIGURE 2 | (A) Schematic: tACS in Parkinson's disease (PD). Abnormal beta oscillations (red line, left and right) are related to rigidity and bradykinesia. Application of tACS with a phase lag of 180° (blue line, right) leads to a reduction of these pathological oscillations (black line, right) by phase cancellation (right). As a result, rigidity and bradykinesia are reduced. Please note that to date phase cancellation has been thought to be able to reduce tremor in PD by affecting tremor related cortical frequencies. To our knowledge, beta frequency has not yet been targeted by NIBS using the phase cancellation concept. **(B)** Schematic: tACS in PD using online readout techniques. Since it has been reported that during tACS application tremor frequency changed in patients with PD, more online readout techniques should be developed to adjust NIBS applications. After application of 20 Hz tACS (see panel **A**), pathological beta rhythm changes its frequency to 15 Hz (red line, left). tACS of 20 Hz with 180° phase lag (blue line, left) looses its effect (black line, left). After online adjustment, tACS shifts to 15 Hz (blue line, right). Pathological beta (red line, right) is again reduced (black line, right). **(C)** Schematic: rTMS in schizophrenia (SCZ). By modulating oscillators of abnormal gamma-band activity (red line, left), amplitude is reduced (black line, right) and related behavioral impairments are reduced.

abnormalities in neuropsychiatric disorders as a treatment strategy. As discussed above, this concept is supported by studies suggesting, for example, that tACS can reduce tremor in PD (Brittain et al., 2013) or that rhythmic TMS can improve both working memory (Barr et al., 2013) and impaired gamma activity in patients with SCZ (Barr et al., 2011). In stroke, NIBS might modulate both oscillatory activity and clinical performance (Dammekens et al., 2014). Taken together, the application of rhythmic NIBS in order to modulate underlying, disease related oscillations is a very promising approach.

Next steps will be the development and evaluation of safe and low-cost applications of patterned NIBS in order to target pathological oscillatory activity to achieve improvement of clinical symptoms of neuropsychiatric patients impacting on their daily life. Demonstrating the expected effects of NIBS in patients might have an incremental impact on treatment of neuropsychiatric disorders and subsequently the health system, as novel devices has been developed for home-based, self-application of NIBS. As soon as such approaches will be proven save in the home-based environment, they may offer a cost-effective strategy to significantly enhance treatment intensity.

Still one can argue critically that oscillatory changes after NIBS application are not a cause but a by-product merely associated with behavioral changes. However, combining NIBS with electrophysiological recordings bears great potential to establish the specificity and reliability of oscillations as biomarkers.

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frontiers in Systems Neuroscience

MINI REVIEW
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Noninvasive brain stimulation for the treatment of auditory verbal hallucinations in schizophrenia: methods, effects and challenges

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This mini-review focuses on noninvasive brain stimulation techniques as an augmentation method for the treatment of persistent auditory verbal hallucinations (AVH) in patients with schizophrenia. Paradigmatically, we place emphasis on transcranial magnetic stimulation (TMS). We specifically discuss rationales of stimulation and consider methodological questions together with issues of phenotypic diversity in individuals with drug-refractory and persistent AVH. Eventually, we provide a brief outlook for future investigations and treatment directions. Taken together, current evidence suggests TMS as a promising method in the treatment of AVH. Low-frequency stimulation of the superior temporal cortex (STC) may reduce symptom severity and frequency. Yet clinical effects are of relatively short duration and effect sizes appear to decrease over time along with publication of larger trials. Apart from considering other innovative stimulation techniques, such as transcranial Direct Current Stimulation (tDCS), and optimizing stimulation protocols, treatment of AVH using noninvasive brain stimulation will essentially rely on accurate identification of potential responders and non-responders for these treatment modalities. In this regard, future studies will need to consider distinct phenotypic presentations of AVH in patients with schizophrenia, together with the putative functional neurocircuitry underlying these phenotypes.

Keywords: transcranial magnetic stimulation, auditory verbal hallucinations, phenotypes, schizophrenia, brain stimulation, brain function

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Introduction

Auditory verbal hallucinations (AVH) are defined as auditive perceptions involving a verbal aspect in the absence of a provoking external stimulus (Aleman and de Haan, 1998). They represent a core symptom of schizophrenia and related spectrum disorders, but they also frequently occur in other psychiatric entities and in the non-psychiatric general population. In schizophrenia the term AVH comprises a multi-dimensional and heterogeneous group of symptoms that can be differentiated by certain phenomenological aspects such as subjective loudness, acoustic clarity, location and subjective reality. About 60–80% of patients affected by schizophrenia experience AVH (Aleman and de Haan, 1998; Hugdahl et al., 2008), such as conversing, commenting or imperative spoken speech in distinct voices. These symptoms, especially when the verbal content is experienced as negative, intrusive or persecutory,

often induce high levels of distress and lead to significant psychosocial impairment. AVH are a highly relevant feature of schizophrenia that have attracted extensive clinical, phenomenological and neurobiological interest, yet treating these symptoms, especially in persons suffering from persistent AVH which do either not or not sufficiently respond to psychopharmacotherapy, is still a major clinical challenge. In approximately 25% of patients with schizophrenia, AVH are refractory to psychotropic drug treatment and can chronically persist (Shergill et al., 1998). Currently, there are no randomized controlled trials available which specifically investigated effects of psychopharmacotherapy (either monotherapy or combined drug regimes) on AVH severity reduction or full symptom remission. In a recent review (Sommer et al., 2012), data from the European First-Episode Schizophrenia Trial (EUFEST) was used to assess effects of five antipsychotic agents on AVH severity. Superiority of one treatment option against another was not confirmed for AVH severity (Sommer et al., 2012). Clinically, clozapine is still the drug of choice for patients with AVH who are resistant to two other antipsychotic agents. At present, no clinical trial has been published that specifically compares the efficacy of clozapine in comparison to other antipsychotic agents in the treatment of drug-resistant AVH.

Transcranial Magnetic Stimulation

Given the need for effective treatment modalities, it is not surprising to see that over the past decade brain stimulation techniques have been increasingly used to ameliorate symptom burden in patients with schizophrenia suffering from persistent and mostly pharmacorefractory AVH. Among these approaches, a possible augmentation strategy for the treatment of psychiatric disorders (in particular catatonia and severe depression) is elctroconvulsive therapy (ECT). For patients with schizophrenia a meta-analysis of 10 double-blind RCT showed a significant effect for ECT (Tharyan and Adams, 2005), although none of the studies provided any specific details on AVH improvement (Sommer et al., 2012). In a recent review Nieuwdorp and colleagues summarized different stimulation methods including transcranial magnetic stimulation (TMS), ECT and transcranial Direct Current Stimulation (tDCS) in patients with medication-resistant psychosis (Nieuwdorp et al., 2015). The authors concluded that currently there is only weak evidence for stimulation techniques to relieve pharmacorefractory psychosis. Specifically considering AVH, further studies are needed to draw any strong conclusions about ECT as a treatment option for patients presenting with persistent AVH.

In the last decade, TMS has evolved into a therapeutic modality for several psychiatric and neurological symptoms. In particular, TMS is widely used to treat patients with major depression, obsessive-compulsive disorder (OCD) and specific symptoms of schizophrenia (AVH and negative symptoms) (Slotema et al., 2010). Its application as an adjunctive therapy is currently proposed by European specialists with evidence level C (Lefaucheur et al., 2014) taking into account that it is generally regarded as safe. We consider the application of TMS for treating individuals presenting with persistent AVH as paradigmatic. The use of TMS impressively illustrates a translational approach from basic neuroscience/neuroimaging to clinical treatment. However, it also illustrates fundamental methodological, neurobiological and phenomenological questions and challenges, which we will refer to in the following paragraphs.

TMS: Putative Mechanisms of Action

TMS is a technique which allows a non-invasive stimulation of cortical neurons through the scalp. Originally, TMS was implemented as a neurophysiological tool for the study of the human motor system (Barker et al., 1985). Put simply, TMS uses a strong pulse of electrical current in a coil which is placed over the brain generating rapidly pulsating magnetic fields, which pass through the scalp, skull, and meninges, into the brain (Wassermann and Zimmermann, 2012). Thus, changing magnetic fields produce electrical impulses that stimulate superficial cortical neurons 2–3 cm below the device (Wassermann and Zimmermann, 2012). Modern devices can generate a rapid succession of pulses, called repetitive TMS (rTMS) by producing a relatively powerful magnetic field (about 1.5–3T), but only lasting very shortly (ms) (George and Aston-Jones, 2010). Frequencies of 1 Hz or lower are considered to be inhibitory, while frequencies of 5 Hz and higher are considered to be excitatory (Aleman, 2013). The specific topology of the induced electrical field in the brain is a source of uncertainty, because it is influenced by the complex shape and diverse conductivity of the cranial contents (Wassermann and Zimmermann, 2012), e.g., cerebrospinal fluid and foraminas in cranial bone. Long-term potentiation (LTP) and long-term depression (LTD) are believed to be key processes underlying long-term effects of rTMS (Chervyakov et al., 2015). *In vitro* experiments of hippocampal slice cultures suggest that rTMS can alter cortical excitability in terms of LTP of synaptic transmission inducing an increase in synaptic strength and postsynaptic AMPA receptor changes (Vlachos et al., 2012). At the level of functional connectivity, long-lasting enhancement is reflected by increased hippocampal-cortical network coupling after rTMS (Wang and Voss, 2015).

How Effective is rTMS in the Treatment of AVH?

As a target region for rTMS in patients with AVH the superior temporal cortex (STC) is of special interest given converging multimodal imaging evidence suggesting a crucial role in AVH generation and perception (Allen et al., 2008; Waters et al., 2012). The rationale for stimulating this region is to inhibit cortical overactivity and potentially influence generative phenomena (i.e., AVH) which are thought to be closely associated with regionally increased cortical activity. Up to now, several randomized sham-controlled studies targeting the left temporoparietal cortex have been conducted and summarized in seven meta-analyses revealing effect sizes (Hedges' "g") ranging from 0.42 (i.e., a close to moderate effect) to 1.04 (regarded as high effect; Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2012, 2014). With the inclusion of the studies with larger patient samples, the mean

weighted effect size of rTMS directed at the left temporoparietal area for AVH appears to decrease over time, although the effect is still significant (Slotema et al., 2012, 2014; Hoffman et al., 2013). Of note, Slotema and colleagues showed that the effect of rTMS was no longer significant at one month of follow-up revealing a mean weighted effect size of 0.40 (95% confidence interval = −0.23–0.102; Slotema et al., 2012). For a detailed description of the included studies, please see tables provided by Slotema and colleagues. Side effects were mild and the number of dropouts in the real TMS group was not significantly higher than in the sham group. Only few MRI studies investigated other regions than the left temporoparietal area as target regions for rTMS. Abnormal activation of the right hemisphere regions such as the inferior frontal gyrus and the postcentral gyrus is a frequently reported finding in patients who experience persistent AVH (Kuhn and Gallinat, 2012). Activation changes have been most consistently shown for areas of the prefrontal and temporal cortices (Allen et al., 2007; Sommer et al., 2008; Raij et al., 2009). Based on former findings in neuroimaging studies that both the right and the left temporal activation are associated with AVH (Shergill et al., 2000; Sommer et al., 2007) three studies directed rTMS at the right comparing with the left temporoparietal gyrus for the treatment of AVH (Lee et al., 2005; Jandl et al., 2006; Loo et al., 2010). According to these studies, no superior effects of right-sided stimulation (Slotema et al., 2014) were observed. Correspondingly, neither stimulation of Brocaś area nor its contralateral homologue was an effective target (Schonfeldt-Lecuona et al., 2004). Overall, these findings support the notion that deficient generation, monitoring and perception of inner speech rather than speech expression are disrupted functions in patients with persistent AVH (Shergill et al., 2000; Wolf et al., 2011). Abnormal STC function clearly plays a critical role in the expression of AVH, especially in those patients presenting with chronic and treatment-refractory symptoms. Recent studies showed that stimulation of this region with low-frequency rTMS may reduce the severity and frequency of AVH in schizophrenia patients, but the duration of the effect of rTMS may be less than one month (Slotema et al., 2012).

Methodological Issues with TMS and the Challenge of Treating Phenotypic Diversity

As briefly discussed in the previous paragraph, it is noteworthy that therapeutic effects of rTMS in AVH patients are not long-lasting, and that along with publication of studies with larger patient populations, the effect size of rTMS over the left temporoparietal area has decreased over time (Slotema et al., 2012, 2014). Several studies published between 2004 and 2014 did not observe beneficial effects of rTMS in the treatment of persistent AVH (Schonfeldt-Lecuona et al., 2004; Slotema et al., 2011; Blumberger et al., 2012; Rosenberg et al., 2012; Bais et al., 2014). Several reasons may account for these phenomena. Two specific aspects of stimulation will be discussed, which may be superior to left sided STC intervention and which may also account for these variable results. Subsequently we will address the problem of the phenotypic diversity which is inherent to AVH both at the neural and phenomenological level.

Is Bilateral Stimulation Superior?

It may be conceivable that bilateral could be superior over unilateral stimulation, especially given known dissociations of left- vs. right-hemispheric function. Up to now, however, only one study examined bilateral rTMS of the TPJ (Bais et al., 2014). The authors suggested that AVH frequency might be one of the most sufficient parameters to measure the responsiveness of left sided rTMS. In comparison, right-sided rTMS allows for a more complete management of AVH in terms of emotional and non-linguistic aspects which are suggested to originate in the right hemisphere. Contrary to their prediction, however, Bais and could not show any beneficial effect of bilateral rTMS in comparison to left sided rTMS and sham in improving AVH (Bais et al., 2014). Neurophysiological aspects such as transcallosal inhibition, and fewer rTMS impulses (50%) in a bilateral design (Thiel et al., 2006; Bais et al., 2014) might account for these negative results.

Is STC stimulation alone sufficient?

The functional dominance of STC stimulation over other brain regions has been questioned by accumulating neuroimaging data acquired in patients with AVH. For instance, an association between AVH-severity and STC gray matter volume loss has been suggested by univariate voxel-based morphometry studies (Modinos et al., 2013). In contrast, using a multivariate statistical approach for structural data analysis, two distinct abnormal structural networks were recently identified in patients with persistent AVH, including a bilateral prefrontal system and a bilateral temporal/medial frontal network (Kubera et al., 2014). The latter structural network also differed between patients with persistent AVH compared to non-hallucinating patients (Kubera et al., 2014). It is possible that unilateral temporoparietal stimulation might not be sufficient to induce a relevant neuronal change in both networks, whose mutual interplay has still to be determined. Also, the relationship between structure and function still remains unresolved, e.g., in individuals with persistent AVH the impact of neural loss to neural network transmission, including effects in more remote neural networks, is unclear.

From a functional point of view, both "symptom capture" (i.e., inferring AVH-related brain activity from symptom occurrence) and "symptom interference" (i.e., inferring AVH-related brain dysfunction from paradigm-driven data) MRI studies have been conducted to investigate neural activation patterns in schizophrenia patients experiencing treatment-resistant AVH (Lawrie et al., 2002; Mechelli et al., 2007; Wolf et al., 2011). The vast majority of these studies focused on brain activity in speech-related pathways (Lavigne et al., 2015), according to the prevailing model of AVH suggesting a link between symptom generation and dysfunctional inner speech perception and monitoring (Hugdahl et al., 2008). From these studies, the left STC emerged as regions linked to AVH and in turn set the rationale for targeted stimulation.

Yet the left temporal cortex, although a crucial neural node for hallucinatory symptom expression, is not the sole region which is thought to be involved in AVH generation and persistence. The prefrontal cortices have been frequently found to exhibit abnormal neural activity in patients with AVH, both at the level of regional function and at the level of functional connectivity (Kuhn and Gallinat, 2012; Alderson-Day et al., 2015). Although the processes subserved by abnormal prefrontal activity in patients experiencing AVH are not fully elucidated at present, several explanations have been put forward, such as deficient attentional and executive control over speech- and self-monitoring relevant brain regions. In addition, converging evidence suggests that AVH are not related to regional brain dysfunction alone, but rather to abnormal neural network coupling in several distinct neural networks including systems engaged in language, attention, executive function, memory and self-referential processing (Stephane et al., 2001; Allen et al., 2008; Wolf et al., 2011; Diederen et al., 2013). Thus, single-site stimulation may not fully cover all key regions involved in AVH pathophysiology. In this regard, bilateral or bifocal stimulation could be a promising approach. Based on the hypothesis of temporal hyperactivity and frontal hypoactivation in schizophrenia patients presenting with AVH, Brunelin and colleagues used a different non-invasive stimulation method, i.e., tDCS (Brunelin et al., 2012). Unlike TMS, in tDCS a weak direct current passes through the brain between two electrodes, i.e., modulation of two spatially remote regions is possible. Brunelin and co-workers used cathodal left temporoparietal junction (TPJ) stimulation and anodal left dorsolateral prefrontal stimulation. After five days of treatment a significant decrease of hallucinatory symptoms was shown, and this effect remained significant three months after stimulation. These findings were recently replicated (Mondino et al., 2015) and provides a promising outlook for further clinical trials. Nevertheless, given that tDCS is a relatively new technique employed in AVH treatment, several stimulation parameters (e.g., electrode placement and stimulation intensity, frequency and duration) have to be investigated in more detail to optimize future treatment options (Koops et al., 2015).

It is noteworthy that although the lateral prefrontal and temporal cortices clearly are involved in AVH generation, there is also good evidence suggesting a role of cortical midline regions in AVH symptom expression. Abnormal cerebral blood flow could also be detected not only in the primary temporal cortex and Broca's area, but also in the cingulate cortex (Wolf et al., 2012; Kindler et al., 2013). In a recent study exploring resting-state functional connectivity of the brain, cross-network abnormalities could be detected between the so called "default mode network" (DMN) and the "salience network," including core midline regions such as the bilateral paracingulate cortex and bilateral anterior cingulate cortex (Alonso-Solís et al., 2015). Of note, DMN subsystems have been essentially involved in self-referential and mnemonic processes (Andrews-Hanna et al., 2010; Sambataro et al., 2013). Abnormal network interactions between the DMN and language-processing and auditory networks could well explain deficient self-monitoring and a lack of self-referential attribution of voices (Northoff and Qin, 2011). This body of evidence indicates important contributions of cortical midline regions to the pathomechanisms of persistent AVH. TMS alone might be insufficient to stimulate these regions in treatment-resistant patients.

The Challenge of Phenotypic Diversity

When treating AVH in patients with schizophrenia using focal stimulation techniques, the clinical endpoint appears to be clearly defined. In the vast majority of cases, this is at least a reduction in overall AVH severity. Yet it should be kept in mind that schizophrenia is a phenomenologically heterogeneous disorder with several distinct phenotypic presentations at both the clinical and neurobiological level, and the very same heterogeneity also applies to persons with chronic AVH. In addition, the multidimensionality of AVH has been long acknowledged by phenomenological research (Kronmüller et al., 2011; McCarthy-Jones et al., 2014), but research has only recently begun to specifically explore therapeutic effects on distinct symptom domains (Leff et al., 2013).

Apart from refining and technically developing stimulation techniques *per se*, a major focus of future research will be the identification of markers which can predict stimulation treatment response. An approach which might prove to be helpful for predicting responders and non-responders in the future is subtyping AVH patients according to both neurobiological and clinical criteria. For instance, it has been attempted, albeit with limited success, to improve responsiveness to rTMS by targeting the site of maximal neural activation associated with the hallucinatory event (Slotema et al., 2011). More recently, Homan and colleagues (Homan et al., 2012) showed that higher resting-brain perfusion as measured with arterial spin labeling in the left STC prior to treatment predicted a clinical response to rTMS (Homan et al., 2012). This marker may guide stratification strategies in future interventional trials. Also, it is important to acknowledge that certain symptom characteristics, such as location of voices in inner our outer space, may map to distinct neural correlates. In this respect, a relationship between white matter volume in the right temporal junction and spatial features such as outer vs. inner location of voices has been identified (Plaze et al., 2011). However, stimulation of the right temporal lobe could not show a superior treatment effect. A possible explanation is that there may well be structural differences between hallucinating characterized by "physical" features with yet unknown consequences for brain function and treatment response. Another explanation for non-response to stimulation could include neural ceiling effects, e.g., related to various degrees of subjective symptom control. Over time, patients with persistent AVH seek for ways of coping with their voices, e.g., by deliberately directing their attentional focus to specific external stimuli (which can be auditory) or by employing individual modes of verbal control. The degree of control over AVH is associated with distinct frontotemporal cortical correlates in contrast to physical or affective symptom dimensions (Wolf et al., 2012). Also, increased frontotemporal connectivity in hallucinating patients is modulated by the degree of control over verbal material (Lavigne et al., 2015). Thus, it is possible that different degrees of control over AVH severity

prior to therapeutic stimulation could influence treatment response.

McCarthy-Jones and colleagues proposed different subtypes of AVH, which might respond to different treatment modalities. These subtypes may be identified at the levels phenomenology, cognition, neurology, etiology, treatment response, diagnosis, and voice hearer's own interpretation (McCarthy-Jones et al., 2014). Particularly, an AVH subtype characterized at a neural level by chronic deafferentiation of the auditory cortex is proposed, according to the hypothesis of AVH as misattributed forms of inner speech (Ford and Mathalon, 2005). This subtype might be specifically responsive to focal stimulation treatment, i.e., rTMS or tDCS. Furthermore, specific subtypes might show both common and distinct regions of activation in both "symptom capture" and "symptom interference" studies, so that future neuroimaging studies may consider specific subtypes in their protocol and report details of AVH phenomenology. The majority of functional neuroimaging studies used total severity and frequency scores of hallucinations (Auditory Hallucinations Rating Scale (AHRS), Auditory Hallucinations Subscale/Psychotic Symptom Rating Scale [AHS/PSYRATS]) as main outcome parameters. To discriminate more fine-grained aspects of change in hallucinations, especially in homogenous subgroups, it might be advantageous to describe different phenomenological dimensions before and their changes after focal therapy. The PSYRATS and a 4-dimensional model within the AHS has previous been recommended to integrate into research and clinical applications (Woodward et al., 2014).

Conclusion

In the past decade non-invasive brain stimulation techniques became increasingly relevant for the treatment of drug-refractory AVH. Evidence for ECT for specifically treating AVH is very limited. There is evidence for beneficial effects of rTMS over left temporal and temporoparietal areas, but effect sizes for this treatment modality are moderate, and beneficial long-term effects are unlikely. It has been suggested that rTMS may reduce aberrant internally generated activity associated with AVH at the site of stimulation. Still, the role of rTMS in changing aberrant network function putatively involved in the generation of AVH has to be clarified. A further major challenge for future research is identifying of patients who do respond to treatment and those who do not or only insufficient. Supported by neuroimaging evidence, the magnitude of left STC activity has been promoted as a potential predictor of clinical improvement. Given the phenomenological diversity of schizophrenia and AVH in particular, it is expected that subtyping patients with AVH will essentially contribute to identify responders from non-responders for focal augmentative therapies. In this respect, in accordance with other authors we strongly advocate further development of reliable and valid psychometric assessments and neurobiological markers paralleling the optimization of future stimulation protocols. Other neuromodulatory interventions, such as tDCS provide very promising data as well but larger trials are needed.

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Prefrontal tDCS Decreases Pain in Patients with Multiple Sclerosis

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Background: In the last few years, transcranial direct current stimulation (tDCS) has emerged as an appealing therapeutic option to improve brain functions. Promising data support the role of prefrontal tDCS in augmenting cognitive performance and ameliorating several neuropsychiatric symptoms, namely pain, fatigue, mood disturbances, and attentional impairment. Such symptoms are commonly encountered in patients with multiple sclerosis (MS).

Objective: The main objective of the current work was to evaluate the tDCS effects over the left dorsolateral prefrontal cortex (DLPFC) on pain in MS patients.Our secondary outcomes were to study its influence on attention, fatigue, and mood.

Materials and Methods: Sixteen MS patients with chronic neuropathic pain were enrolled in a randomized, sham-controlled, and cross-over study.Patients randomly received two anodal tDCS blocks (active or sham), each consisting of three consecutive daily tDCS sessions, and held apart by 3 weeks. Evaluations took place before and after each block. To evaluate pain, we used the Brief Pain Inventory (BPI) and the Visual Analog Scale (VAS). Attention was assessed using neurophysiological parameters and the Attention Network Test (ANT). Changes in mood and fatigue were measured using various scales.

Results: Compared to sham, active tDCS yielded significant analgesic effects according to VAS and BPI global scales.There were no effects of any block on mood, fatigue, or attention.

Conclusion: Based on our results, anodal tDCS over the left DLPFC appears to act in a selective manner and would ameliorate specific symptoms, particularly neuropathic pain. Analgesia might have occurred through the modulation of the emotional pain network. Attention, mood, and fatigue were not improved in this work. This could be partly attributed to the short protocol duration, the small sample size, and the heterogeneity of our MS cohort. Future large-scale studies can benefit from comparing the tDCS effects over different cortical sites, changing the stimulation montage, prolonging the duration of protocol, and coupling tDCS with neuroimaging techniques for a better understanding of its possible mechanism of action.

Keywords: pain, attention, multiple sclerosis, transcranial direct current stimulation, dorsolateral prefrontal cortex

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INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive inflammatory disease of the central nervous system, and represents the major cause of non-traumatic disability in young adults (Noseworthy et al., 2000; Compston and Coles, 2008). During the course of the disease, the patients may develop sensorimotor, cognitive, emotional, and behavioral symptoms. For instance, although MS was previously considered a painless disease, chronic pain has been recently reported as a debilitating symptom (Ehde et al., 2005), with a prevalence varying between 29 and 86% (O'Connor et al., 2008). The lower limbs dysesthesias remain the most common and difficult to treat painful symptoms, attributed to demyelination and axonal degeneration processes involving the central sensory pathways (O'Connor et al., 2008). Psychiatric comorbidities are also common (Marrie et al., 2015). In particular, anxiety and depression were found to occur in about 21.9 and 23.7% of MS patients, respectively (Marrie et al., 2015). Moreover, up to 75% of MS patients can face fatigue at some point during the disease course; such a symptom was found to have a drastic impact on their quality of life (Chalah et al., 2015). Furthermore, abnormalities in the attentional capacities have been described in MS patients (Urbanek et al., 2010; Crivelli et al., 2012; Omisade et al., 2012; Vázquez-Marrufo et al., 2014; Ayache et al., 2015).

The interaction between pain and attention has gained an increasing interest in the last decade. Although pain serves as a warning signal for responding to potential hazards, its relationship with the intensity of a stimulus is not linear. It is rather modulated by several factors, among which attention appears to play a major role (Van Damme et al., 2010). On the one hand, distraction was documented to decrease the perceived intensity of provoked pain (Legrain et al., 2002). On the other hand, pain can capture the attentional processes, in a way that prohibits good performance on cognitive tasks, even with a voluntary neglect of the nociceptive stimuli (Eccleston and Crombez, 1999; Legrain et al., 2009a,b; Van Damme et al., 2010). In this perspective, the neurocognitive model of attention to pain explains the aforementioned interaction by two modes of selection: the top-down attention, which prioritizes relevant information and prevents irrelevant stimuli such as pain from capturing attention, and the bottom-up attention by which unintentional stimulus captures the attention (Legrain et al., 2009a).

The current advances in neuroimaging and neurophysiological modalities have unveiled the key role of the dorsolateral prefrontal cortex (DLPFC) in the circuits of pain (Lorenz et al., 2003), fatigue (Chalah et al., 2015), depression (Gobbi et al., 2014), and attention (Petersen and Posner, 2012), including the attentional circuit dedicated to noxious stimuli (Legrain et al., 2009a). Among the available literature regarding experimental pain, one study has revealed negative correlations between the activation patterns within the DLPFC bilaterally and each of pain intensity and unpleasantness (Lorenz et al., 2003). Here, the DLPFC was thought to modulate pain perception through corticosubcortical and corticocortical pathways. In addition, DLPFC seems to be a major component of the so-called cortico-striato-thalamo-cortical fatigue loop in MS (Chalah et al., 2015). Moreover, the middle frontal gyrus, which embeds the DLPFC, was found to be selectively related to depression in MS (Gobbi et al., 2014). Furthermore, DLPFC constitutes a main component of the attentional circuits, particularly the fronto-parietal executive control network (Petersen and Posner, 2012). This was based on lesions studies in human where the DLPFC appears to be involved in switching from one set of tasks to the other (Petersen and Posner, 2012). Nevertheless, experimental research investigating the interaction between bottom-up and top-down attention has highlighted the role of DLPFC in processing the painful stimuli (Legrain et al., 2009a). By maintaining the attentional load, this cortical area prioritizes goal-relevant information in order to prevent the attentional capture by pain (Legrain et al., 2009a). Therefore, one can assume that acting on DLPFC might have an impact on pain perception, attentional resources, mood, and fatigue.

Noninvasive brain stimulation (NIBS) is currently being investigated for the management of neuropsychiatric symptoms when pharmacological interventions fail. Among those techniques, transcranial direct current stimulation (tDCS) has gained a particular interest in recent years, and appears to be a promising tool for the treatment of several neurological disorders. It acts by changing the cortical excitability (Nitsche and Paulus, 2000, 2001; Nitsche and Fregni, 2007; Nitsche et al., 2008), notably by depolarizing (activating) and hyperpolarizing (inhibiting) the cortical circuits, in the case of anodal and cathodal stimulation, respectively.

In the present work, we applied anodal tDCS over the left DLPFC. Our primary endpoint was to evaluate its effects on neuropathic pain in MS patients. Our secondary outcomes were to assess its impact on attention, mood, and fatigue.

MATERIALS AND METHODS

Ethics Statement

This is a prospective, randomized, cross-over, sham-controlled study, conducted according to the declaration of Helsinki, and approved by the local ethical committee (CPP-Ile de France VI, registered as N° 2012-A00721-42). The trial is registered at the Deutsches Register Klinischer Studien (drks-neu.uniklinik-freiburg.de) and has the following registration number: DRKS00005296. All participants were well instructed about the protocol and voluntarily gave their written informed consent prior to inclusion.

Study Participants

Patients were enrolled by M.A., M.S., D.D., and A.C. from the Neurology department of Henri Mondor Hospital, Créteil, France, between November 2012 and November 2014 according to the following criteria: (i) a definite MS diagnosis according to the 2010 revised McDonald criteria (Polman et al., 2011); (ii) age between 18 and 70 years; (iii) right handedness based on the Edinburgh inventory (Oldfield, 1971); and (iv) a history of neuropathic pain since more than 3 months as per the Neuropathic Pain Symptom Inventory (NPSI; Bouhassira et al., 2004), with an intensity >40 on the visual analog scale from 0

to 100 (VAS_{0-100}), obtained as the average of daily scores over a representative week.

Exclusion criteria consisted of the following: (i) MS relapses within the last 2 months; (ii) changes in pharmacological and physical therapies during the last month; (iii) the presence of comorbid neurodegenerative or psychiatric disorders; (iv) history of substance abuse; (v) absence of measurable pain related evoked potentials (PREPs) at the right hand; (vi) severe deficit in the visual acuity or fields as documented by an ophthalmic exam; and (vii) severe right upper limb impairment as per the Medical Research Council scale for muscle power (MRC) (Medical Research Council, 1981). For the latter, we applied the MRC score to the four muscle groups involved in pinching, wrist extension, forearm flexion, and arm abduction, so that the sum of their scores could vary between 0 (null strength) and 20 (full strength); an MRC score <12 excluded the individual from participation.

A standard neurological examination was performed in all patients including a documentation of the disability level based on the expanded disability status scale (EDSS; Kurtzke, 1983), and a thorough pain evaluation.

tDCS

A battery driven multi-channel direct current stimulator (Starstim, Neuroelectrics, Barcelona, Spain) delivered the direct current over the scalp through sponge electrodes (surface area = 25 cm^2), soaked in a saline solution to minimize the risk of skin irritation (Palm et al., 2014). The stimulation electrodes were directly positioned on an adult sized cap worn by the patients, and labeled according to the 10–20 EEG system of electrode positioning (Starstim, Neuroelectrics, Barcelona, Spain). To stimulate the left DLPFC, the anode was placed over F3, and its corresponding cathode over the right supraorbital region (**Figure 1**). The used current intensity was 2 mA (total current density over the stimulated area: 0.06 mA/cm^2) which is below the threshold for tissue damage (Poreisz et al., 2007; Nitsche et al., 2008). For the active stimulation, the current was ramped up during the first 15 s to a maximum of 2 mA that was maintained throughout the 20-min stimulation session. As for the sham stimulation, the current was ramped down immediately after ramping up in order to achieve an effective blinding (Gandiga et al., 2006; Ambrus et al., 2012).

Sham or active anodal tDCS blocks were tested in a random order and were held apart by at least 3 weeks. Each block consisted of three consecutive daily tDCS sessions. The stimulations were performed by well-trained physicians. The sessions took place in a quiet and illuminated room. The patients were at rest in an armchair and were not performing any cognitive task. Only the performing physician (S.S.A) was aware of the stimulation mode (real or sham tDCS). The evaluators (U.P and M.A.C) and the patients were blind to it.

Primary Outcomes: Pain Scales

For pain evaluation, we relied on the self-reported VAS_{0-100} and the short version of the Brief Pain Inventory (BPI). The latter is a validated and reliable tool to measure pain intensity and its interference with patient's life (Cleeland and Ryan, 1994).

Secondary Outcomes

Cognitive Task

Attention was evaluated using a computerized test: The Attention Network Test (ANT; Fan et al., 2002). Briefly, this test evaluates the three main attentional networks: the alerting network that consists of controlling vigilance and task performance, the orienting network responsible for the orientation to external stimuli, and the executive function network in charge of conflict resolution (Fan et al., 2002; Petersen and Posner, 2012). The test was performed in a quiet room, with the participants sitting in front of a monitor aligned to their midsagittal plane. The stimulus consists of a row of five horizontal black arrows, against a white background: a "central" arrow surrounded on each side by two others called "flankers" which can be pointing left- or right-ward. Several possible conditions arise: a "congruent" condition takes place when the flankers and the central arrow are in same direction; an "incongruent" condition occurs when the flankers and the central arrow are in opposite direction; and a "neutral" condition occurs when the flankers are replaced instead by four strokes. The participants indicated the direction of the central arrow by clicking on the left or right mouse buttons, with either the right index or the right middle finger, when the central arrowhead pointed to the left or right, respectively. During the total duration of the test, the subjects are asked to fix a central cross, and are informed about a warning "cue," which consists of a star-shaped signal that may precede the stimulus in question, and thus might either help or not in localizing the latter. Here, four possibilities exist: "no cue" condition when there is no preceding signal, "center cue" condition when it appears at the center of the screen, "double cue" condition when signals are simultaneously provided above and below the central cross, and a "spatial" cue condition when the signal is presented either up or down the cross. We used the 1.3.0 version of ANT, which includes one practice sequence (24 trials), and three identical sequences of 96 trials each, separated by an optional resting period. The participants should answer correctly as fast as possible, and the test provides the mean accuracy (MA) and the mean reaction time (MRT), which reflect the errors rate and the time required by the participant to answer, respectively. Moreover, all conditions are analyzed to assess the integrity of the attentional networks. For instance, the alerting network is evaluated when the participant fixes the central cross; the orienting network is put into play when the warning signal is presented prior to the stimulus; and the executive function network is recruited when the subject is trying to solve the conflict and takes a decision in order to answer.

Neuropsychological Assessment

Mood and fatigue were evaluated using the 14-item Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1986) and the 21-item Modified Fatigue Impact Scale (MFIS), respectively (Fatigue guidelines development panel of the multiple sclerosis council for clinical practice guidelines, 1998; Téllez et al., 2005). MFIS accounts for the physical (9 items), cognitive (10 items), and psychosocial (2 items) components of fatigue.

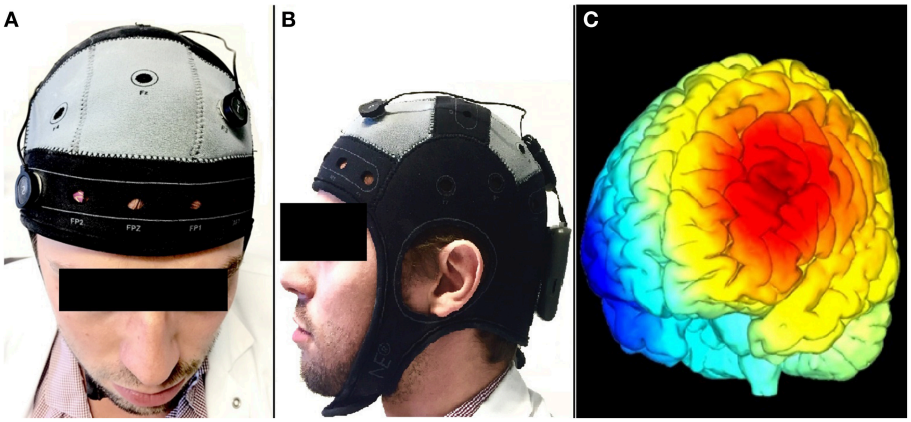

FIGURE 1 | An illustration of the tDCS montage in this study (Starstim, Neuroelectrics, Barcelona, Spain); with a cathode over AF8 (A), an anode over F3 (A,B) according to the international 10–20 EEG system. A simulation of the electric field generated between F3 (in red) and AF8 (in blue) is shown in **(C)**.

Neurophysiological Testing

Pain related evoked potentials (PREPs)

PREPs can be generated at the cortical level by a variety of noxious stimuli (Kakigi et al., 2005; Arendt-Nielsen and Andersen, 2006), namely the lasers (Arendt-Nielsen and Chen, 2003). Their amplitudes serve as physiological correlates for the amount of attention paid toward noxious stimuli, and reflect the functionality of the involved neural networks (Garcia-Larrea et al., 2002; Lorenz and Garcia-Larrea, 2003). A concentric planar electrode—which was previously found to be an alternative to laser in inducing PREPs—has served the purpose in this work (Kaube et al., 2000; Lefaucheur et al., 2012).

The first step consisted of defining the pain perception threshold (PPT). The PPT was determined by the method of limits, which consists of raising the stimulus intensity from zero to the point where the stimulus is perceived as painful sensation at intensity of 60–70 on VAS_{0-100}. The threshold was determined three times. The average of the three trials was defined as the PPT.

Stimulation was carried out using a concentric electrode designed to excite the superficial skin layers, hence the nociceptive axons (Lefaucheur et al., 2012). Stimuli were applied at the first dorsal interosseous space of the right hand, the cutaneous area located on the dorsal and lateral aspect of the hand between the extensor pollicis longus tendon and the extensor indicis tendon. A single stimulus was a train of three pulses that lasts 0.5 ms, with an inter-pulse interval (IS) of 5 ms.

After determining the PPT, two sets of twenty stimuli were performed at irregular intervals, at $VAS_{60-70.}$The PREPs were recorded via 10 mm Genuine Grass Gold Cup Electrodes (Grass Products, Astro-Med, Inc., Natus Neurology, Warwick, RI 02886 U.S.A.), fixed to the scalp surface using a special paste (Grass Products, Astro-Med, Inc., Natus Neurology, Warwick, RI 02886 U.S.A.). The electrodes were positioned as the following: the recording one at Cz (international 10–20 EEG system of electrode positioning), the reference one at the left earlobe, and the ground one with a Velcro strap around the right forearm (Ref NT-S07ALPINE ground electrode with Velcro Strap, Alpine Biomed, Skovlunde, Denmark). In addition, electro-oculogram was obtained via pre-gelled adhesive surface electrodes (Ref 9013S0242, Alpine Biomed, Skovlunde, Denmark) placed at the right infraorbital lateral margin.

The recorded signal was bandpass filtered at 0.5–30 Hz and stored for analysis using a Keypoint machine (Dantec Dynamics, Bristol, United Kingdom). The final step consisted of averaging the signals offline, and excluding the contaminated recordings (saccadic eye movements or blinks, and raw signals above 70 V). We then analyzed the collected N2-P2 responses and measured their baseline-to-peak amplitudes, peak-to-peak amplitudes, and latencies.

Frontal midline theta activity

The frontal midline theta (FmΘ) is an oscillatory activity in the theta band (4–7 Hz) that appears in the medial frontal region at any time during the performance of a cognitive task, reaching 6–7 Hz in frequency and 30–60 mV in amplitude (Ishihara and Yoshi, 1972; Mizuki et al., 1980). We looked for this activity by recording EEG during the second ANT sequence. The recording electrodes were located on the patients' cap at Fpz and Fz (according to the international 10–20 EEG system of electrode positioning), and connected to the recording device (Starstim, Neuroelectrics, Barcelona, Spain). The raw EEG signals were stored for offline processing and analysis. These signals were then pass-band-filtered in the frequency range [0.5–30 Hz] to keep only the rhythms of interest delta, theta, alpha and beta.

An important step before doing any analysis would be to reject ocular and blink artifacts that are highly abundant in raw data. For this, prior to any analysis, we applied on all data an algorithm that detects, localizes, and rejects artifacts in a single-channel biosignal. An example of the artifact rejection is shown in **Figure 2**.

EEG analysis

EEG analysis was performed by T.A. and A.B. To obtain a good estimate of the percentage held by the dominant

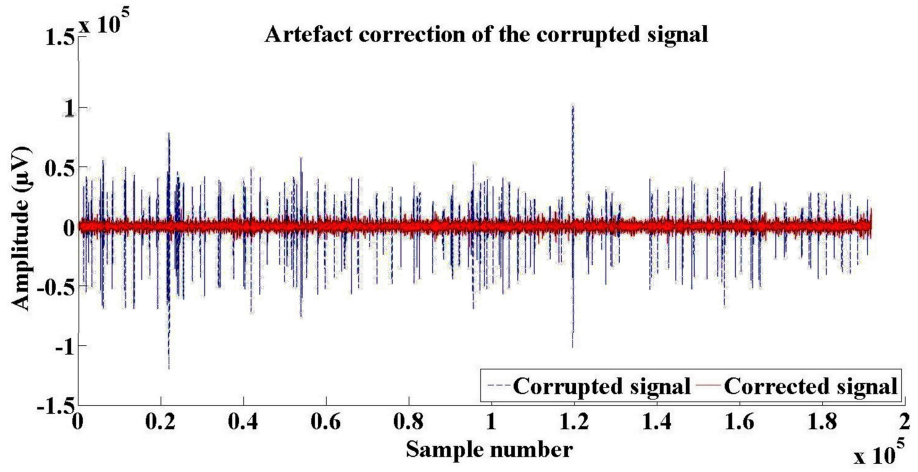

FIGURE 2 | An example of artifact rejection in a single EEG record.

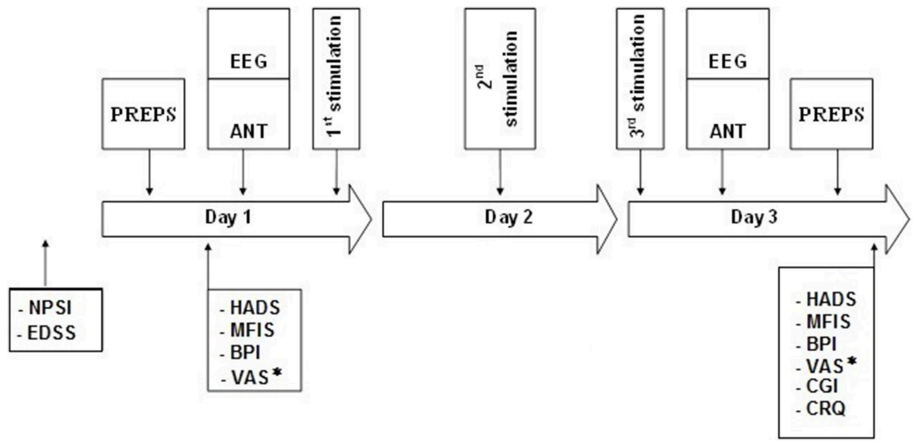

FIGURE 3 | Schematic diagram of the experimental protocol. Two tDCS blocks, each consisting of 3 consecutive daily stimulations of either sham tDCS or active tDCS (randomized order); held apart by a 3-week interval.ANT, Attention Network Test; BPI, Brief Pain Inventory; CGI, Clinical Global Impression; CRQ, Comfort Rating Questionnaire; EEG, recording at Fpz and Pz during ANT; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; NPSI, Neuropathic Pain Symptoms Inventory; PREPs, Pain Related Evoked Potentials; VAS*, Visual Analog Scale for pain assessed 7 days prior to the first stimulation session (D1) and 7 days after the last stimulation session (D3) of each block.

rhythms (delta, theta, alpha, and beta) in a given raw EEG signals we determined the frequencies that dominate each signal.

First, the signals were band-pass filtered in the frequency bands [0.5–3.5 Hz], [4–7 Hz], [8–12 Hz], and [13–30 Hz] corresponding to the rhythms delta, theta, alpha, and beta respectively. To take into account the difference in the amplitudes of these rhythms, we determined the gradient of their amplitudes, looked for their envelopes, and calculated the modulus of the Hilbert transform of the gradients in question (Marple, 1999). At each sample of the given EEG signal, we selected the maximum modulus. Finally, the percentage of each frequency band in the given EEG signal of each patient was determined.

Experimental Protocol

After the inclusion session, patients were randomized to receive either sham or active tDCS block (**Figure 3**). The randomization schedule was generated by U.P. prior to the beginning of the study using a dedicated software ("true" random number generation without any restriction, stored in a computer until the patient was assigned to the intervention).

Keeping in mind the fluctuating nature of neuropathic pain, and the effects of circadian rhythm on attentional capacities, the patients underwent the experimental protocol at the same time of the day (Knight and Mather, 2013). They were also asked to restrict stimulants consumption, like caffeine or nicotine, at least 3 h prior to their appointment. No blocks were performed during summer time to avoid any influence of temperature on fatigue (Chalah et al., 2015).

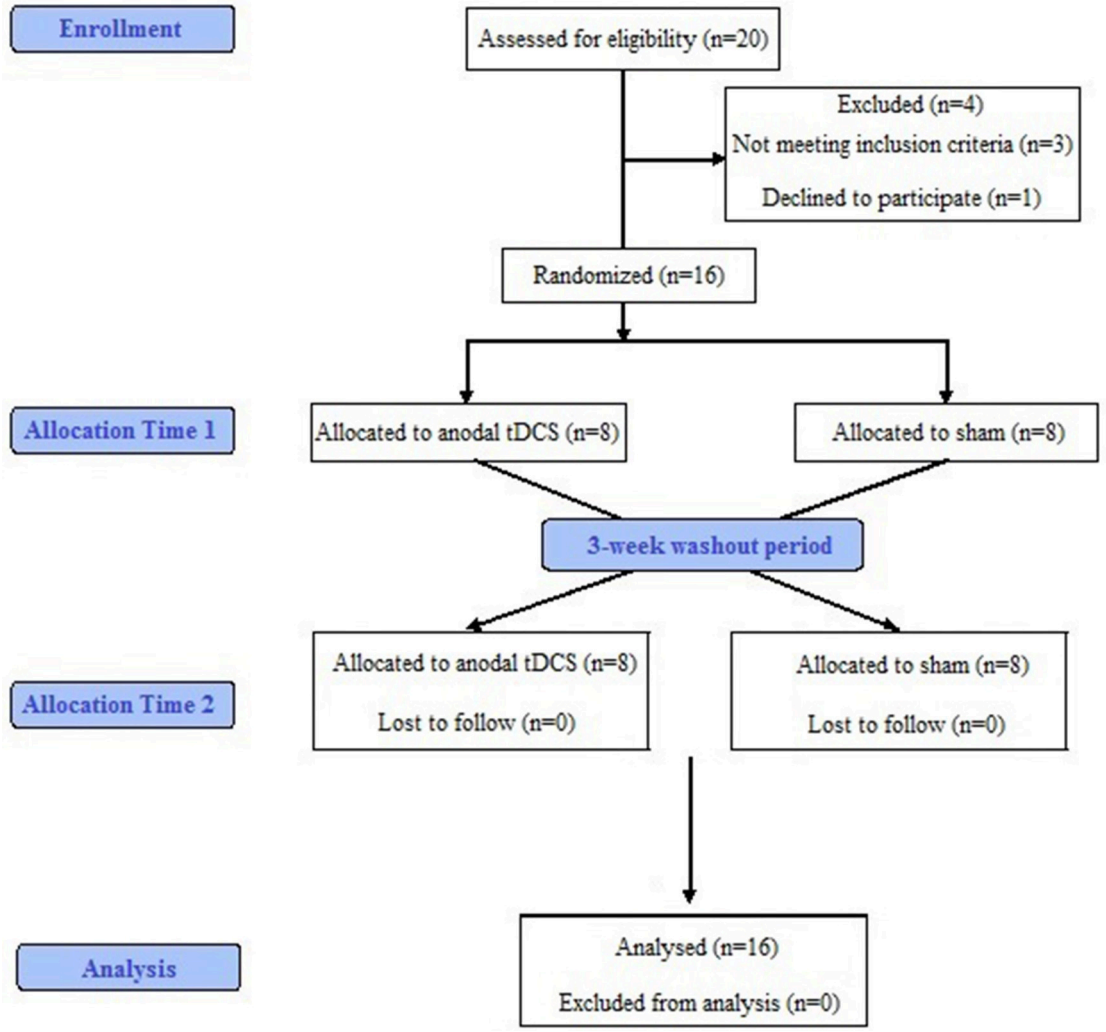

FIGURE 4 | Schematic flow chart of patients through the study.

The patients daily recorded the average of their pain intensity 1 week before and 1 week after each block using VAS_{0-100}. At the first day of each block (D1), they were asked to fill questionnaires for pain (BPI), fatigue (MFIS), anxiety and depression (HADS). This was followed by PREPs recording, the performance of ANT test, and finally the tDCS session. The latter was repeated at the second (D2) and third (D3) day of each block. At D3, the above-mentioned evaluations were repeated following the stimulation session, and the patients' degree of satisfaction regarding the protocol was assessed using the Comfort Rating Questionnaire (CRQ) and the Global Clinical Impression (GCI). At the end of each block, the patients were asked to guess the mode of stimulation (active/sham). A schematic diagram is shown in **Figure 3**.

Data Analysis

For the ANT parameters, we excluded from the analysis the reaction times of trials with either error or with a reaction time value above or below the mean ± 2 standard deviations (SD). Statistical analyses were performed using the StatView and InStat software. Our Data followed normal distributions according to the method of Kolmogorov and Smirnov. Data collected before and after each block were analyzed with paired *t*-tests, and those with a $p < 0.05$ were considered significant. This included PREPs (amplitudes and latencies), ANT parameters (MA and RT), frontal theta activity percentages, and self-rating questionnaires scores for pain (VAS_{0-100}, BPI), fatigue (MFIS), anxiety and depression (HADS).

RESULTS

Demographic and Clinical Data

Twenty MS patients were enrolled, and four were excluded (one declined to participate, and three were not eligible). Sixteen patients (13 women, 3 men, mean age 48.9 ± 10.0 years, age range 38–67 years) completed the study (**Figure 4** illustrates the flowchart of all participants). All had neuropathic pain; their mean NPSI was 5.12 ± 2.4

at enrollment. Their mean EDSS was 4.25 ± 1.4. Eleven patients had relapsing remitting MS (RRMS), four were in the secondary progressive phase (SPMS) and one had a primary progressive type (PPMS). The mean disease duration was 11.8 ± 9.4 years and the progressive phase duration was 6 ± 3.2 years.

All patients had concomitant medication intake, consisting of antiepileptic drugs (nine patients; one of them with two drugs), antidepressants (nine patients, one of them with two drugs), opioids (five patients, one of them with two drugs) and immunomodulating agents (13 patients). Pharmacological treatment was continued and kept stable throughout the experimental protocol.

Adverse Effects, Comfort Rating, and Blinding Integrity

After both active and sham stimulation, six patients reported insomnia. Nausea was reported by five patients after active stimulation and by four patients after sham stimulation. Severe headache occurred in three patients after active stimulation and in one patient after sham stimulation. Phosphenes were reported by one patient after sham stimulation.

No significant difference was found between both conditions regarding the CRQ sum scores during ($p = 0.96$) and after stimulation ($p = 0.43$). No significant differences were observed between both stimulation conditions on the overall discomfort ($p = 0.79$) or the mean GCI ($p = 0.82$; Friedman test). Details are provided in **Table 1**.

Pain Perception

The mean VAS_{0-100} pain ratings 7 days before and 7 days after stimulation showed significant decrease after active tDCS ($p = 0.024$), but no change after sham tDCS ($p = 0.66$). Analogously, the mean VAS_{0-100} pain ratings for days 1–3 before and after stimulation showed significant decrease after active tDCS ($p = 0.021$), and no improvement after sham tDCS ($p = 0.56$).

Active stimulation resulted in a significant improvement of BPI global score ($p = 0.02$), and its interference subscale ($p = 0.01$), but had no significant effects on the severity subscale. Sham did not have any significant effects on BPI scores or its subscales. Pain scores are found in **Table 2**.

Cognitive Results

There were no significant changes in any of the ANT parameters after both sham and active stimulation (**Table 3**).

Neuropsychological Scores

The baseline mean global MFIS score, HADS anxiety and depression subscales were 52.6 ± 12.2, 9.2 ± 4.0, and 6.6 ± 3.2, respectively.

No significant differences were observed following both stimulation conditions for the MFIS total scores, HADS total scores and subscales. The neuropsychological scores are detailed in **Table 4**.

TABLE 1 | Confort rating questionnaire (CRQ) and global clinical impression (GCI) for sham and active tDCS.

	Sham	tDCS	paired *t*-test
CRQ sum scores during stimulation	18.3 ± 12.3	19.1 ± 11.5	*P = 0.96*
CRQ sum scores after stimulation	20.7 ± 13.8	17.5 ± 9.6	*P = 0.43*
Overall discomfort after stimulation	2.4 ± 2.0	2.6 ± 2.3	*P = 0.79*
Mean GCI after stimulation	4.6 ± 0.8	4.6 ± 0.9	*P = 0.82*

Neurophysiological Testing

PREPs

PREPs results did not significantly differ between active and sham stimulation (**Table 5**).

EEG Results

A trendwise or significant increase in the theta band was observed following sham and active stimulation, respectively. Theta Fpz showed a trendwise increase after sham stimulation ($p = 0.09$), and theta Fz showed significant increase after sham stimulation ($p = 0.04$). After active stimulation, theta Fpz and Fz increased by trend ($p = 0.09$ and $p = 0.09$, respectively; **Table 5**).

DISCUSSION

This study aimed to explore the impact of prefrontal tDCS on pain in 16 MS patients. Active anodal but not sham tDCS showed significant analgesic effects on VAS_{0-100} pain ratings in the first 3 days and over 1 week after stimulation. These effects were further reflected by a significant decrease in the BPI total score and its interference subscale following only active stimulation. No relevant changes in BPI severity subscale were found after either stimulation conditions. Similarly, neither intervention had any effects on PREPs (amplitudes and latencies), ANT parameters, fatigue and mood scales. Lastly, a trendwise or a significant increase in the frontal theta activity was observed following active or sham stimulation, respectively.

Effects on Pain

The most prominent effect of tDCS treatment was analgesia. Such findings are of high interest and in line with previous studies. In fact, the DLPFC is known to have a crucial role in modulating pain (Lorenz et al., 2003). Interestingly, changes in pain perception following tDCS have been documented in several experimental protocols where anodal tDCS over the DLPFC increased the pain thresholds induced by electrical and heat stimuli in healthy volunteers (Boggio et al., 2008; Mylius et al., 2012).

As for the BPI scale, the fact that anodal tDCS over the prefrontal cortex ameliorated the interference but not the severity subscale might be accounted by the pathophysiologic mechanisms of pain. Actually, a pain matrix was conceptualized and includes three interacting networks (Garcia-Larrea and Peyron, 2013). A first order nociceptive network comprises

TABLE 2 | VAS and BPI scores (Mean ± SD) before and after sham and active tDCS.

	Before sham	After sham	Paired *t*-test	Before tDCS	After tDCS	Paired *t*-test
VAS mean/7days	52.1 ± 19.6	50.3 ± 19.7	*P = 0.66*	51.2 ± 19.2	43.1 ± 26.2	*P = 0.02*
VAS mean/Day 1–3	48.8 ± 22.0	51.3 ± 18.8	*P = 0.56*	53.1 ± 20.2	43.1 ± 26.2	*P = 0.02*
BPI global score	9.9 ± 3.5	9.2 ± 3.4	*P = 0.19*	9.2 ± 3.4	8.2 ± 3.5	*P = 0.02*
BPI severity subscale	4.8 ± 2.4	4.6 ± 2.1	*P = 0.40*	4.8 ± 2.4	4.3 ± 2.1	*P = 0.15*
BPI interference subscale	5.0 ± 1.5	4.6 ± 1.6	*P = 0.18*	4.5 ± 1.6	3.9 ± 1.6	*P = 0.01*

TABLE 3 | ANT results (Mean ± SD) before and after sham and active tDCS.

	Before sham	After sham	Paired *t*-test	Before tDCS	After tDCS	Paired *t*-test
ANT alertness	61.7 ± 60.5	58.8 ± 66.0	*P = 0.78*	36.5 ± 42.0	52.1 ± 36.0	*P = 0.08*
ANT orientation	53.7 ± 33.2	53.4 ± 27.5	*P = 0.98*	41.0 ± 30.5	50.2 ± 27.4	*P = 0.33*
ANT conflict	143.0 ± 67.9	141.8 ± 53.2	*P = 0.95*	143.1 ± 75.8	153.9 ± 69.0	*P = 0.43*
ANT mean reaction time	768.3 ± 95.0	766.1 ± 130.3	*P = 0.94*	725.4 ± 93.8	742.3 ± 99.7	*P = 0.38*
ANT accuracy	86.1 ± 21.7	90.2 ± 14.6	*P = 0.43*	92.4 ± 9.2	88.4 ± 15.0	*P = 0.17*

TABLE 4 | Neuropsychological results (Mean ± SD) before and after sham and active tDCS.

	Before sham	After sham	*t*-test	Before tDCS	After tDCS	*t*-test
Mean HADS total score	14.4 ± 5.9	14.5 ± 6.5	*P = 0.80*	14.1 ± 6.3	13.6 ± 5.8	*P = 0.52*
Mean HADS anxiety	8.1 ± 3.4	8.3 ± 3.9	*P = 0.70*	7.7 ± 3.0	7.6 ± 3.6	*P = 0.90*
Mean HADS depression	6.3 ± 3.0	6.2 ± 3.3	*P = 0.81*	6.4 ± 3.9	6.0 ± 3.3	*P = 0.35*
MFIS global score	48.2 ± 15.5	47.4 ± 17.7	*P = 0.76*	49.5 ± 14.4	49.0 ± 15.2	*P = 0.42*

the posterior operculoinsular area receiving spinothalamic projections. A second order network consists of the posterior parietal, prefrontal and anterior insular areas, and is responsible of the transition from cortical nociception to conscious perception. A third network is composed of the orbitofrontal, perigenual and limbic areas, by which the pain perception can be modified in function of expectations, emotions and beliefs. Therefore, our results suggest that tDCS could have acted on the second and third order networks of the pain matrix where the prefrontal cortex majorly contributes (Garcia-Larrea and Peyron, 2013).

Effects on Attention

Concerning attention, ANT variables did not significantly change after any of the tDCS interventions. In fact, we hypothesized that tDCS over the DLPFC could improve attentional capacities by modifying the sensitivity of stimulus-specific neural responses, in a way that enhances the top-down selection type or inhibits the bottom-up one; notably, by amplifying or inhibiting the activity of neurons which respond, respectively, to relevant or irrelevant stimuli (Desimone and Duncan, 1995). In accordance with our speculation, anodal tDCS over the left DLPFC have found to improve the attentional bias acquisition in one study (Clarke et al., 2014), and sustained attention in another one (Nelson et al., 2014). However, the lack of significant improvement of ANT parameters in our study can be explained by many facts. First, ANT is known to represent a complex task which measures three different attentional networks and hence involves several cortico-cortical and cortico-subcortical connections. Second, in contrast to previous tDCS studies in healthy subjects, MS patients are known to have a dysfunction in the attentional networks, notably in the alerting and/or the orienting ones (Urbanek et al., 2010; Crivelli et al., 2012; Omisade et al., 2012; Vázquez-Marrufo et al., 2014; Ayache et al., 2015) which might have prevented tDCS from causing any improvement. Third, our tDCS design might not have been optimal to ameliorate ANT variables. It is noteworthy that a lateralization in the attentional performance exists between left and right hemispheric structures (Corbetta and Shulman, 2002; Raz and Buhle, 2006; Lückmann et al., 2014). In fact, the left and right hemispheres are thought to be involved in phasic and tonic alertness, respectively (Raz and Buhle, 2006). In this model, the right DLPFC has an executory capacity which enables it to monitor the attentional performance and hence regulates it accordingly, while the right inferior parietal region seems to have a role in endogenous and exogenous alerting. In line with this topography, one study found that anodal tDCS over the right frontal cortex (F10 of the 10–10 EEG system of electrodes positioning) could improve the alerting network of attention (Coffman et al., 2012). Another study compared the effects of anodal tDCS over different cortical targets in terms of attentional improvement and showed significant effects following the stimulation of the right posterior parietal cortex (PPC) but not the left DLPFC (Roy et al., 2015). This suggests that unlike our design, which targeted the left hemisphere, stimulation of

TABLE 5 | Neurophysiological (EEG and PREPS) results (Mean ± SD) before and after sham and active tDCS.

	Before sham	After sham	Paired *t*-test	Before tDCS	After tDCS	Paired *t*-test
Theta Fpz	51.1 ± 14.6	58.9 ± 10.2	*P = 0.09*	53.8 ± 13.9	62.1 ± 11.1	*P = 0.09*
Theta Fz	53.9 ± 9.8	59.3 ± 7.9	*P = 0.04*	54.9 ± 15.1	62.6 ± 10.5	*P = 0.09*
Mean N2 latency	118.9 ± 34.8	131.7 ± 25.6	*P = 0.16*	138.1 ± 44.6	141.8 ± 33.2	*P = 0.66*
Mean P2 latency	178.0 ± 48.8	187.0 ± 36.0	*P = 0.41*	202.2 ± 58.5	199.6 ± 45.9	*P = 0.80*
Mean N2 amplitude	11.3 ± 7.6	14.1 ± 6.5	*P = 0.16*	12.6 ± 9.9	12.0 ± 7.4	*P = 0.77*
Mean P2 amplitude	10.5 ± 4.3	10.4 ± 7.6	*P = 0.96*	15.1 ± 10.7	13.2 ± 9.4	*P = 0.57*
Mean N2-P2 amplitude	21.4 ± 8.9	22.4 ± 9.2	*P = 0.64*	25.2 ± 9.0	23.6 ± 13.0	*P = 0.50*

the right fronto-parietal structures might have better effects on attention. Fourth, our protocol consisted of performing ANT before the first stimulation session (D1) and after the last one (D3) of each block, but did not contain a "within-day control" of attention. This was based on the hypothesis that a tDCS-induced cumulative effect might result from the repetition of the stimulation sessions. However, three consecutive daily sessions might not be enough to induce such an effect, and therefore a within-day control for attention would have revealed better outcomes. Fifth, concerning the tDCS montage adopted in this study, the anode was placed at the left DLPFC while its reference electrode was the right supraorbital region. We should note that the chosen reference is not neutral. In fact the orbitofrontal cortex has an important role inemotional and cognitive processing, including the attentional processes to emotional stimuli. Therefore, applying a cathodal stimulation on that region might have impacted our results.

These data altogether suggest that future studies might benefit from comparing the effects of tDCS over different cortical areas (e.g., left/right DLPFC and left/right PPC), prolonging the duration of the stimulation period, adding a within-day control for attention, and adopting a different reference site, before drawing any conclusion.

Effects on Mood and Fatigue

As for mood changes, although there are evidence regarding the antidepressant effects of anodal tDCS over the DLPFC (Kalu et al., 2012; Loo et al., 2012; Berlim et al., 2013; Brunoni et al., 2013), the lack of mood changes in our patients cohort can be attributed to the short stimulation period adapted in this study. In this perspective, depression studies have shown dose-dependent effects of tDCS in mood improvement that could extend over several weeks. Our results are supported by another study where no improvement in mood scores has occurred following five tDCS sessions over the left DLPFC (Saiote et al., 2014).

Concerning fatigue, we found no effects of tDCS on the MFIS scores. A lack of improvement in fatigue following tDCS has already been reported by two studies (Ferrucci et al., 2014; Saiote et al., 2014).

Effects on Neurophysiological Parameters

PREPs

PREPs amplitudes were not changed following both active and sham tDCS. Although PREPs can correlate with the subjective pain sensation, it is commonly accepted that PREPs amplitude reflects the integrity of the spino-thalamo-cortical tract (Casey et al., 1996; Wu et al., 1999; Garcia-Larrea et al., 2002). In this view, most of the neuroimaging studies have demonstrated that MS patients with neuropathic pain had several demyelinating lesions within the spinal cord, brainstem, and thalamus (Seixas et al., 2014). Furthermore, PREPs amplitude is known to depend on the attentional level toward the stimulated limb (Garcia-Larrea et al., 2002), in this context, attentional dysfunction has been frequently reported in MS patients. Taken together, these disturbances might have prohibited tDCS from having any effect on PREPs parameters in our cohort.

EEG

As for the frontal midline theta activity, their increase following both stimulation blocks can be explained by different approaches. In fact, anxiety improvement has previously been correlated with the appearance of such waves following anxiolytic treatment (Mizuki et al., 1983, 1989). In addition, an emotionally positive state was found to be associated with theta power in frontal midline leads (Aftanas and Golocheikine, 2001). In this perspective, it might be possible that medical care itself, regardless of stimulation block type, had accounted for a subtle decrease in patients' anxiety, despite the absence of any significant changes in HADS scores.

Limitations

It is important to note that, in our patients' cohort, the observed tDCS effects could have been influenced by antiepileptic treatments. The latter are known to inhibit long-term-potentiation induced neuroplasticity changes by blockade of voltage-gated ion channels (Nitsche et al., 2012). However, in most of the studies dealing with chronic neuropathic pain, patients commonly suffer from a severe pain which is resistant to multiple drugs. Particularly, the available tDCS studies for central neuropathic pain have included patients taking antiepileptics, antidepressants, and opioid analgesics (Fregni et al., 2006; Soler et al., 2010; Wrigley et al., 2013). Similar to our work, the authors asked their patients to keep their routine medications throughout the study period. Another limitation would be the lack of functional or structural neuroimaging data in our work. Future studies can benefit from combining imaging with tDCS application, in order to understand the mechanisms of action of tDCS on the studied brain networks, and to correlate the clinical

response to gray matter and white matter pathologies (Chalah et al., 2015). In addition, the small sample size and heterogeneity of our MS cohort could have prohibited the emergence of any positive effect in terms of attention, mood and fatigue. Finally, MS-related symptoms can fluctuate during the course of the disease; such a fluctuation should be taken into account prior to the interpretation of any intervention results. In this context, our study could have benefited from testing the difference between baseline scores prior to tDCS and sham conditions. However, we believe that our inclusion criteria (e.g., the presence of a neuropathic pain since more than 3 months with an intensity greater than 40 on VAS; the absence of MS relapses since at last 2 months, a stable therapy since 1 month) might have restricted such an influence. We also controlled for the impact of some variables on attention, pain, and fatigue; namely by restricting the consumption of psychostimulants, and performing the stimulation block at the same time during the day, with no blocks occurring in summer.

AUTHOR CONTRIBUTIONS

MA, MS, DD, and AC: enrolled patients from the neurology department of Henri Mondor Hospital. SA, UP, and MC: performed the stimulation sessions and collected the data. SA and JL: designed the study, developed the methodology, interpreted the data and wrote the final draft. MC and UP: wrote the first draft. TA and AB: analyzed the EEG data.

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METHODS
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Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols

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The effect of transcranial direct current stimulation (tDCS) is cumulative. Treatment protocols typically require multiple consecutive sessions spanning weeks or months. However, traveling to clinic for a tDCS session can present an obstacle to subjects and their caregivers. With modified devices and headgear, tDCS treatment can be administered remotely under clinical supervision, potentially enhancing recruitment, throughput, and convenience. Here we propose standards and protocols for clinical trials utilizing remotely-supervised tDCS with the goal of providing safe, reproducible and well-tolerated stimulation therapy outside of the clinic. The recommendations include: (1) training of staff in tDCS treatment and supervision; (2) assessment of the user's capability to participate in tDCS remotely; (3) ongoing training procedures and materials including assessments of the user and/or caregiver; (4) simple and fail-safe electrode preparation techniques and tDCS headgear; (5) strict dose control for each session; (6) ongoing monitoring to quantify compliance (device preparation, electrode saturation/placement, stimulation protocol), with corresponding corrective steps as required; (7) monitoring for treatment-emergent adverse effects; (8) guidelines for discontinuation of a session and/or study participation including emergency failsafe procedures tailored to the treatment population's level of need. These guidelines are intended to provide a minimal level of methodological rigor for clinical trials seeking to apply tDCS outside a specialized treatment center. We outline indication-specific applications (Attention Deficit Hyperactivity Disorder, Depression, Multiple Sclerosis, Palliative Care) following these recommendations that support a standardized framework for evaluating the tolerability and reproducibility of remote-supervised tDCS that, once established, will allow for translation of tDCS clinical trials to a greater size and range of patient populations.

Keywords: tDCS, clinical trials, attention deficit hyperactivity disorder, depression, multiple sclerosis, palliative care

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Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation (NIBS) technique that utilizes low amplitude direct currents (typically less than 2.5 mA current and 0.08 mA/cm^2 average electrode current density) to induce changes in cortical excitability. Advantages of tDCS compared to other methods of NIBS, such as transcranial magnetic stimulation (TMS), include ease-of-use, low cost, and tolerability (Vanneste et al., 2010). Using clinical grade equipment and following strict protocols with trained operators, tDCS has been tested in hundreds of clinical trials and is considered to be both safe and well-tolerated for study in a wide range of subjects (Nitsche et al., 2008; Brunoni et al., 2012b; Kalu et al., 2012).

tDCS can influence sensory, motor, cognitive and psychiatric processes that could be applied directly to the treatment of common yet refractory symptoms that represent major areas of unmet treatment need, such as depressed mood, pain, fatigue, sensory and motor recovery, and cognitive impairment (Ball et al., 2002; Fregni et al., 2006; Mori et al., 2010, 2013; Andrews et al., 2011; Acler et al., 2013; Brunoni et al., 2013b; Cuypers et al., 2013; Bennabi et al., 2014), typically occurring in the context of a neurologic or psychiatric condition.

Remote Delivery Will Expand tDCS Clinical Study

Neurophysiologic and clinical trials with tDCS increasingly reinforce that efficacy increases with multiple sessions (Mori et al., 2010, 2013; Acler et al., 2013; Ferrucci et al., 2014; Meesen et al., 2014; Tecchio et al., 2014), with effects thought to be cumulative. Many clinical investigators apply tDCS in conjunction with a behaviorally-based treatment approach to improve outcome (Demirtas-Tatlidede et al., 2013; Martin et al., 2013b; Brunoni and Vanderhasselt, 2014; Brunoni et al., 2014; Flöel, 2014), which must be repeated alongside tDCS. The clinical utility of tDCS must be established through trials that are sufficiently-powered, with adequate dose (Peterchev et al., 2012) and session number, and with precise protocol control. However, multiple sessions require subjects to repeatedly travel to the clinic for each treatment, placing significant and often insurmountable burden to patients and their caregivers, at the same time associated with significant provider time and cost, especially as the sample size increases (Brunoni et al., 2012a; Holland and Crinion, 2012; Ferrucci et al., 2014; Meesen et al., 2014; Shiozawa et al., 2014; Vaseghi et al., 2014). For example, in a sample of 64 subjects treated for depression, Loo et al. administered 30 sessions across 6 weeks (Loo et al., 2012), followed by up to 20 maintenance treatment sessions spaced over 6 months (Martin et al., 2013a). Similarly, during the 6 month follow up of a depression trial, Valiengo and colleagues showed a dropout rate of 17 of 42 subjects—with almost all dropouts citing the burden of regular visits to the clinic (Valiengo et al., 2013).

A remedy to this feasibility problem is controlled remote tDCS application, with a common protocol that ensures safe, well-tolerated and reproducible remotely-supervised tDCS. Combining this remote approach with behaviorally-based treatments (e.g., cognitive or physical rehabilitation exercises completed at home, or behavioral therapy delivered through remote, web-based platforms) will allow investigators to reach subjects either through satellite clinic locations or directly from their home or care facility.

While there has not yet been a clinical trial involving remotely-supervised tDCS, the home use of tDCS over a 3 year period has been reported as both safe and effective in the case of a patient with schizophrenia through 20 minute daily sessions administered by a medically licensed caregiver (Andrade, 2013).We propose here a protocol for remotely-supervised delivery of tDCS for clinical trials, with the expectation of maintaining the same level of uniformity and compliance that would be seen with tDCS sessions administered in the clinic. This step represents an extension of currently-accepted tDCS methodology to allow for trials to include more subjects and to remove any logistical limits on the number of sessions studied.

The approach proposed for remotely-supervised tDCS can be applied to double-blind trials. tDCS clinical trial devices have been developed which deliver active or sham stimulation depending on the individual subject code keyed in, leaving both device operator and subject blinded to treatment assignment. There is no reason why blinding should be any less available when the subject (or proxy) operates the device under remote supervision.

The Potential and Limitations of tDCS Away From Clinic

Below, we outline a set of what we consider to be essential features for this next step of remotely-supervised tDCS delivery. While the tDCS may be self- or proxy-administered, an important distinction is the difference with this controlled and remotely-supervised extension as compared to direct home use. One recent report described the challenges of prescribing tDCS directly for self-administered home use, without remote supervision. Using a crossover design to treat pain in patients with trigeminal neuralgia, investigators (Hagenacker et al., 2014), instructed subjects and one other adult to apply tDCS at home using a device pre-programmed to alternate active and sham stimulation across 14 sessions over 2 weeks, recording any adverse effects in a diary. All subjects tolerated the stimulation well with no adverse events reported; active treatment was found to be effective in reducing pain. However, many subjects reported difficulty with the tDCS application with an associated high dropout rate (41%). The authors concluded that a more specific and detailed education and training protocol could improve delivery. Of further concern, there was minimal guidance or structure during the course of sessions, possibly leading to variability of method across subjects and no explicit safety monitoring.

It is clear that a structured protocol is needed to identify subjects who are appropriate candidates for remote study, and to ensure that they—or a proxy who will administer the tDCS for them (e.g., caregiver)—are adequately trained. This training and certification, must be gauged against the usability of the (specially-designed) device and headgear, the likelihood that the subject may fluctuate in ability to operate the equipment

(e.g., due to fluctuations in physical or mental state), the risks associated with the specific trial, and other relevant study factors such as the nature of ongoing monitoring.

As a qualifier, specialized equipment designed for this remote study purpose is a minimum requirement. State-of-the-art clinical tDCS equipment and accessories have been developed and validated in controlled clinical trials, with trained operators. It is not safe or prudent to simply provide subjects with specialized clinical equipment, including devices and headgear, not designed for home use. Doing so without accounting for variability in skill, training, and environment puts subjects at risk and compromises reproducibility (e.g., dose control). The distinction between medical equipment designed for professional operators vs. subjects and their caregivers is evident across physical medicine, and is no less important for tDCS. It is misguided to conflate the inherent simplicity and tolerability of clinical tDCS with the assumption that devices not designed for subject use applied by untrained operators pose no risk (Bikson et al., 2013) and allow for reproducible protocols (Peterchev et al., 2012).

Our guidelines are built around ongoing supervision in real-time, even with subjects who have completed training and demonstrated competency to self-administer. While the level of supervision may vary across patient group or risk level at the subject level, we believe that consistency is essential for every tDCS session to ensure safety and tolerability, as well as to maintain the standards of administration set by tDCS sessions in the clinic.

Requirements for Remotely-Supervised tDCS: Essential Features

The recommendations listed here are governed by the principle that remote tDCS administration must be safe, structured and reproducible across study sites. Items are generally categorized by training of staff and subjects/caregivers, design of headgear and stimulators, and ongoing monitoring. These items are interrelated and are itemized here for emphasis of key points—in clinical trial design they will be implemented holistically.

Training of the tDCS Research Staff

Study research staff will first be trained in tDCS treatment technique and in administering tDCS to others. Staff will be trained using standard-operating-procedures (SOP) specifying all subject interactions as well as device usage. In terms of subject interaction, study research staff will be trained to monitor for study-specific "stop" criteria following a decision-tree-based flowchart that allows for evaluation of eligibility to continue at each progressive step. At baseline visits (in clinic) tDCS research staff will complete a checklist to screen subjects for at home tDCS (see **Figure 1** for an example).

Following training on screening procedures, study research staff will be briefed on the usage of the device and the location of headset placement. In addition, selected research staff will be trained with and have access to a guide that details (e.g., the device manual), in a step-by-step fashion, the procedures that are required to configure and program devices prior to release to subjects, for example programming device unlock codes for one-time use to be provided prior to each session. Prior to releasing a device to a subject, selected research staff must program the intensity, duration, and condition (active or sham) of each planned session, along with code that limits the number and frequency of sessions. In the case of code-based session release, research staff will be instructed to withhold any one-time use codes until subject device placement and setup are deemed appropriate.

Research staff will be trained in the preparation and testing of any devices and accessories (e.g., kits) release to subjects, as documentation of material release. Through the duration of the study, technicians will be trained to monitor subjects for any unexpected adverse events (e.g., atypical discomfort) or misuse of the device. At the end of the study, technicians will be instructed on how to evaluate retrieved physical device materials (e.g., headgear/stimulator condition, expendables) and download any data stored on the device (e.g., completion codes for each subject's study sessions, stimulation history of each code issued) as relevant to confirm compliance (**Figure 2**).

In addition to training specific to the implementation of remotely-supervised tDCS as describe above, the clinical research

Subject take-home tDCS checklist

Subject: _____ Date: _____

Assessor: _____

The following abilities should be demonstrated:

Head and Electrode Preparation	**Satisfactory / Comments**
Parting hair to expose stimulation area (if applicable) and gently swabbing the skin with alcohol	
Check the skin for signs of redness, cuts, grazes, pimples, etc.	
Check the electrodes for signs of wear and tear	
Prepare sponges with the correct amount of saline (approx. 6 mL for each side of the sponge)	
Correctly insert electrodes into the sponges (check for right surface facing up and orientation of sponge)	
Correctly attach the sponge electrodes onto the headband	
Correctly place and secure the band on the head with the electrodes in the right position	
Adjust band placement as needed	
Machine Preparation and Stimulation	
Correctly connect the leads to the stimulator (red wire must be inserted into the red slot and black wire into the black slot; red = ANODE, black = CATHODE)	
Correctly connect the leads to the electrodes on the head (anode = left, cathode = right) and place leads over the head crosswise	
Understanding the electrode contact quality read-outs and adjusting the electrode and headband accordingly, adding saline if necessary	
Correctly entering the activation code to initiate stimulation	
During Stimulation	
Remain seated, relaxed and unoccupied during the stimulation	
Monitor contact quality and add saline at designated intervals	
After Stimulation	
Removing the electrodes, disposing of sponges and cleaning of electrodes	
Recharge/replace batteries when required	

☐ The subject was assessed to be competent at delivering tDCS

☐ The subject is not competent at delivering tDCS and needs to be reassessed

Signed by:

Name: _____ Date: _____

FIGURE 1 | Example of subject checklist.

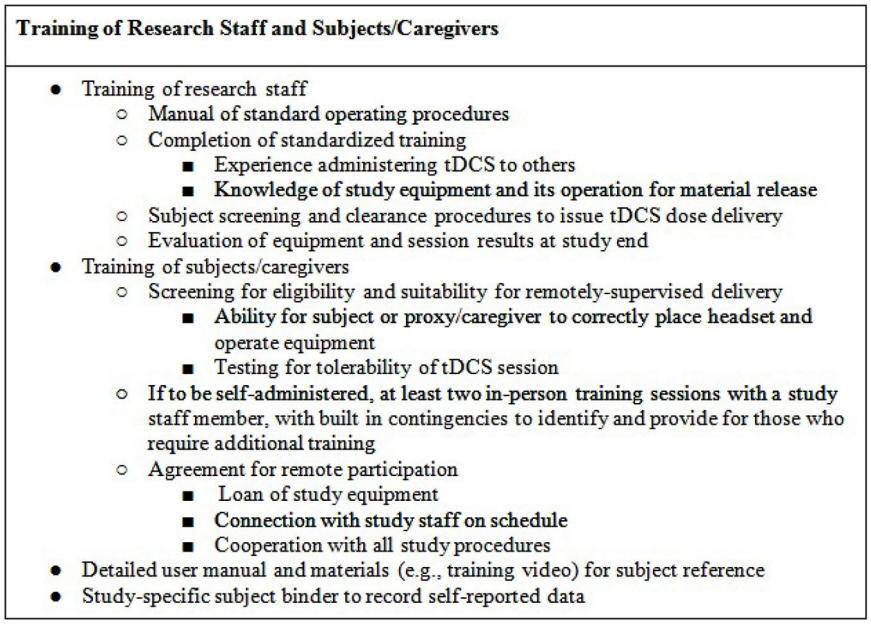

FIGURE 2 | Guidelines for training.

team needs to be skilled in other aspects of clinical trial methodology, including screening of subjects, monitoring of subject progress and evaluation of outcomes.

Initial and Ongoing Assessment of the User's Capability to Participate in tDCS Remotely

A precisely defined protocol (decision-tree-based flowchart) will be closely followed through the duration of the study for each subject. Study "stop" criteria (**Figure 3**) will be reviewed at each stage of the trial: screening, baseline, study sessions, and follow-up. If stop criteria are met at any time throughout the study, the session and/or trial participation will be terminated as specified in the protocol. Following an initial screening, at least one baseline visit will confirm the subject's tDCS aptitude and tolerability. Before any subject is sent home with a device, it will be determined whether the subject-or designated proxy- can properly follow the steps to ensure correct electrode preparation and placement, low impedance and safe removal of the device, and whether the subject can tolerate the stimulation period.

Throughout the study, general compliance will be maintained through stop criteria that exclude subjects who continually fail to set up a device properly or fail to attend regularly scheduled sessions. In addition, if any subject reports an unexpected level of discomfort, pain, or desire to withdraw, the session and/or ongoing study participation may be terminated. At the end of the study, the record of completed and uncompleted sessions, recorded by the device itself, will be reviewed for all subjects who successfully met study criteria. This will be used to determine both individual subject and overall trial compliance based on pre-determined criteria.

Supportive Training Procedures and Materials (Including Assessments of the User and/or Caregiver)

The protocol will be supported by a manual of operating procedures for study staff. For designs with remote supervision of self- or proxy-administered tDCS, that there be at least two in-person training sessions with study staff, including training and practice for the real-time remote supervision procedures (e.g., a training session with a study staff member that includes connection to another remotely-located study staff member via secure internet-based video conference).

For subjects who meet criteria for study continuation, subsequent sessions will be completed with the remote technician alone, with the nature and length of ongoing monitoring to be specific to the subject or trial. For instance, some subjects may require remote monitoring indefinitely, while other trials may use remote monitoring for a training period only.

The protocol will include sequential safety, tolerability and compliance "stops" administered by the supervising study staff throughout the course of the treatment sessions to ensure appropriate use. For instance, potential concerns include failure to place the headset and electrodes correctly, selecting incorrect electrode polarity, inadequate electrode saturation, lack of compliance, and loss of precision in electrode placement.

Each subject will be provided with supportive and readily-accessible training materials (**Figure 2**). These should include an instruction manual (potentially supported with an instructional video) and a method to self-report (electronic or binder). These materials are designed as a resource to the subject to reference or confirm study details. In addition, they serve the purpose of remotely training subjects or caregivers who look to clarify

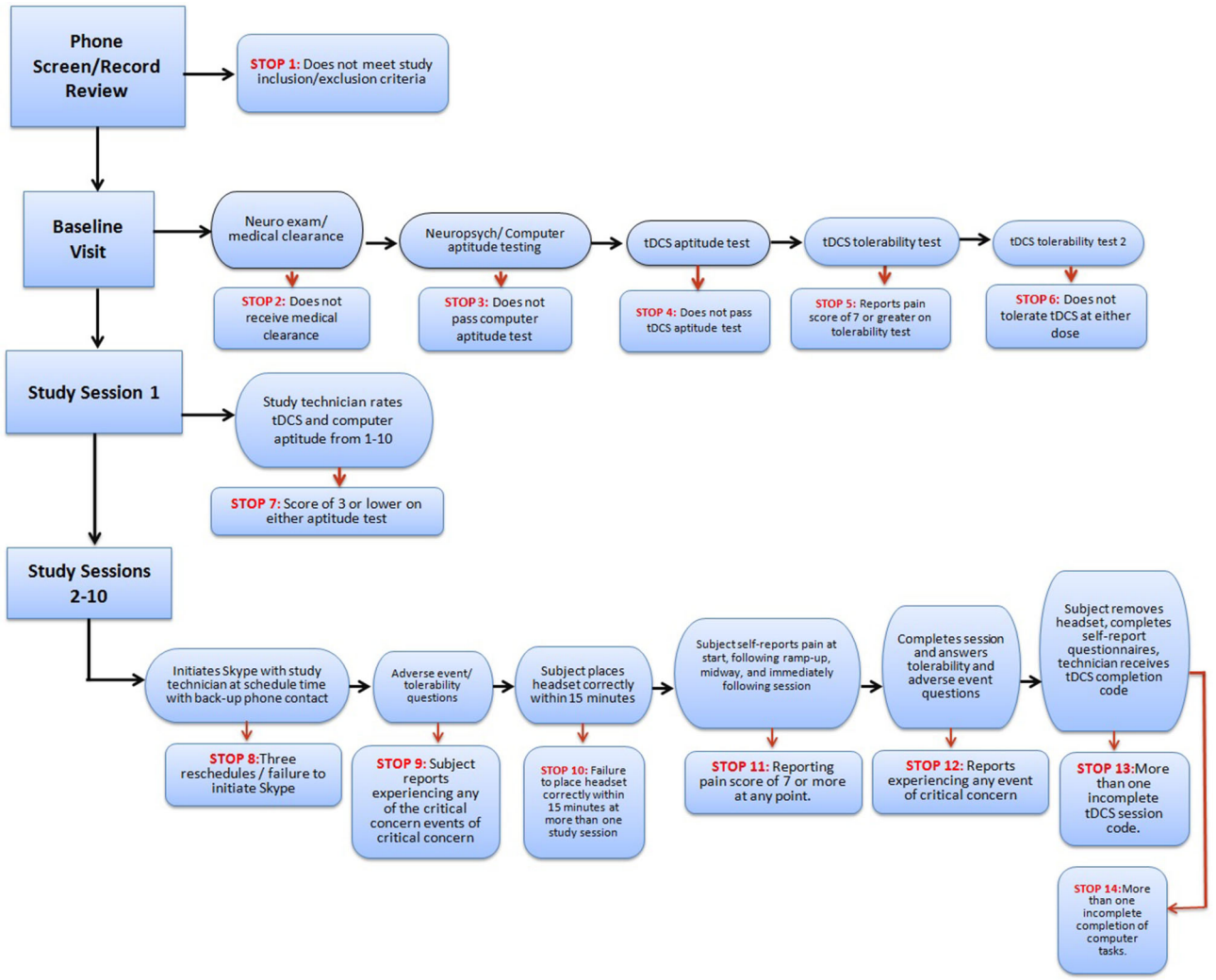

FIGURE 3 | Example of study flowchart with stop criteria.

items of set-up or device usage. The self-report binder will provide the subject with forms that measure adverse events, assess tolerance, along with study-specific measures (e.g., mood). While the manual and video (if used) will serve as ongoing training procedures, the self-report forms will enable the subject and caregiver to assess the experience throughout the study. Any remotely-delivered adjunctive behavioral therapy (e.g., cognitive or physical training) will be trial-specific with a supplemental protocol and procedures.

Simple and Fail-Safe Electrode Preparation and Positioning

The essential aspects of reproducible tDCS dose (defined in Peterchev et al., 2012) are electrode preparation and montage (addressed in this section) and waveform (addressed in the next). Remotely-supervised tDCS administration would reduce barriers to reliably apply tDCS away from the treatment center.

The headgear should be designed to allow simple and consistent placement of electrode at desired locations on the scalp (**Figures 4**, **5**)—for example headband snaps for the sponges to be placed on the headband to ensure consistent correct placement.

Subjects will be screened for aptitude with the specific headgear as part of inclusion/enrollment. Participation is contingent on the ability to properly apply the headset and correctly operate the device. The headgear may be marked in a way that facilitates reliable setup, for example the headset will be labeled "RED" and "BLACK" to confirm that color coded cables are properly placed, ensuring anode (RED) and cathode (BLACK) placement (white can be substituted for red if color blindness is a concern). The headset should be designed to fit reliably on the head, for example designed with a market to align with the bridge of the nose at midline. Headsets may come in multiple sizes and/or allow adjustment by research staff. The device includes an impedance meter and will not allow access until headgear and electrodes are accurately and correctly placed.

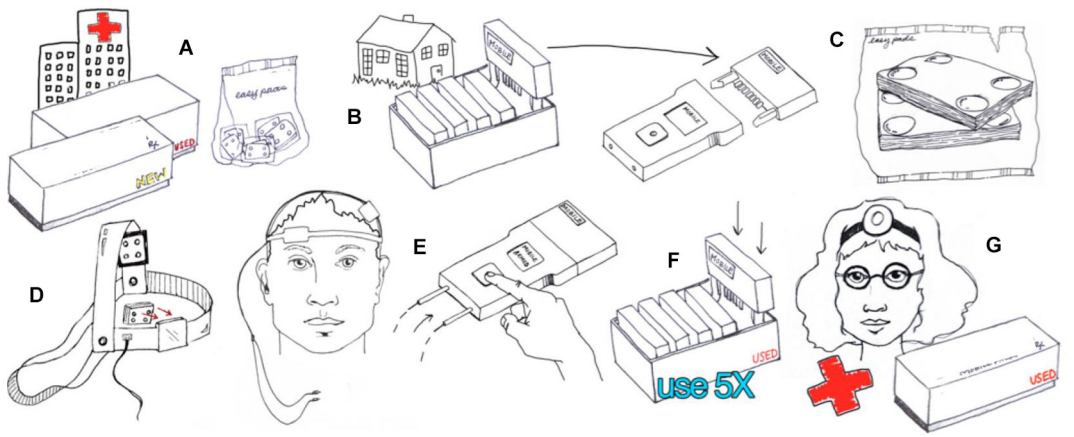

FIGURE 4 | Example of hardware-based waveform control. Users are provided with an individual device and accessories such as the 5x-Session Home Kit **(A)**The subject checks in with the supervisor before and after each session **(B)**. The supervisor unlocks operation before each session by providing a code **(B)**. The subject enters only the code provided with no access to device programming or stimulation settings. The subject uses custom fit headgear to position electrodes **(C,D)**. The device automatically collects compliance data and may also prompt the user for information **(E)**. Details of implementation will be customized to each clinical trial while maintaining the principles of supervised neuromodulation **(F,G)**. *(Image courtesy of Soterix Medical Inc.)*

The headset should be designed to minimize error in electrode placement, ideally allowing just the montage designed for the specific trial (**Figure 6**), e.g., bifrontal montage (for dorsolateral prefrontal cortex target application) or M1-SO montage (for motor cortex target applications).

Subjects/proxies should be provided with kits which include all of the necessary supplies for the entire study or until expendable can be replenished (by either a visit to the clinic or visit by study personnel to the subjects' home or care-facility). Components should be labeled properly in order to simplify application, minimize confusion, and prevent error (e.g., mark each pair of sponges by session number). The subject manual should clearly explain the contents of the kit and the correct use of each component.

Also of note, re-use of sponges across subjects is not hygienic. Re-use of the sponge across sessions, even when cleaned, is not recommended for supervised home use- single-use sponges increase tolerability, cleanliness, and reproducibility. Medical grade sponges are required to comply with biocompatibility requirements, and labeling for re-use would require testing under the intended conditions of use—which are complex and variable in the case of home-application. Reliable control of cleanliness, much less contamination, would prove difficult in home use (would not for example be reliably detected by impedance check or remote observation).In addition, attempt to remediate these sponge re-use concerns would increase the operator and patient burden for monitoring and preparation (e.g., concerns about storage, residue from skin/hair product).

Strict Dose Control for Each Session

Control of stimulation parameters is the second essential aspect after electrode placement. For tDCS essential parameters are the intensity, duration (along with any ramp), and condition (active or sham) of stimulation. For multiple sessions, the number and interval of sessions is critical. For remotely-supervised tDCS, limitations on the number and timing of sessions, along with control of each session intensity and duration is pivotal (**Figure 6**). Providing subjects with clinical stimulators that do not limit either is not safe or supportive of reproducible protocols.

Two general approaches to control stimulation parameters under remotely supervised-tDCS can be considered. In the first case, "hardware" based limitation (**Figure 4**) provides subjects with equipment that is pre-programmed to provide a limited number of sessions with limited interval. For example, the stimulator will provide only 10 sessions, with pre-set intensity, duration, and condition, with a maximum of one session every 23 h. Once 10 sessions have exhausted, the device no longer provides output until the entire hardware or a component (storage disk) is replaced. With "hardware" limitations, it is not necessarily possible to remotely stop use before the 10 sessions are activated. The Soterix Medical/Neuroconn Mobile transcranial Direct Current Stimulator (Mobile) and Magstim/Neuronica HDC-Kit are example of "hardware" based limitation. Subjects or caregivers are required to return to the clinic to replenish expended hardware—supervisors may be provide a "pack" containing multiple dose-control hardware units (e.g., 10 storage disks with 10 sessions each for 100 sessions) but this effectively extends the window where control of dose is limited.

In the second case, "software" based limitation (**Figure 5**) subjects are provided with a device which is deactivated until a code is provided by the research staff. The code typically unlocks a single session which a pre-set duration and intensity. After a single discharge, the device is inert until a new code is provided. This allows the remote supervisor to tightly control compliance, for example not providing a code until proper electrode set-up is confirmed by video,

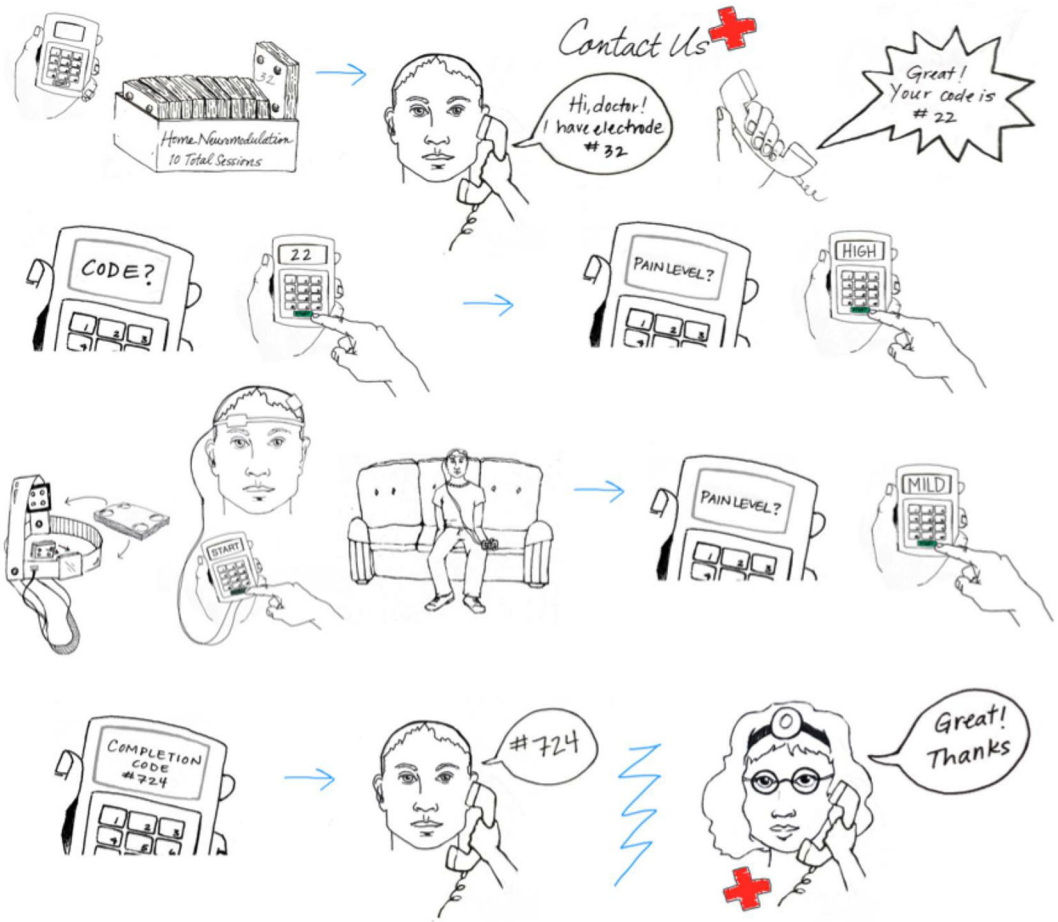

FIGURE 5 | Example of software-based waveform control. Users are provided with an individual stimulator, a discharge key, and accessories such as the 5x-Session Home Kit. The supervisor limits stimulation by programming the discharge key. The subject plugs the discharge key into the device and presses a single button to activate stimulation. The subject uses custom fit headgear to position electrodes. The device automatically collects compliance data which is stored in the discharge key. Details of device implementation will be customized to each clinical trial while maintaining the principles of supervised neuromodulation. *(Image courtesy of Soterix Medical Inc.)*

provides an opportunity for supervisor to directly interact with subject and gather feedback and data for each trial. In this situation, the remote supervisor may vary the provided code based on subject experience. Soterix Medical transcranial Direct Current Stimulator mini-Clinical Trials system (Mini-CT) is one example of "software" based limitation. Given stimulators can be programmed with excess of codes (e.g., thousands), there is no need for subjects to return to the clinic to replenish hardware.

In both "hardware" and "software" based governing for remote supervision, the subject or caregiver does not program session intensity of duration which enhances safety and reproducibility. In case of blinded treatment, the subject may not know which device/code is real or sham treatment. Double blinding may also be implemented by blinding the remote supervisor.

The user manual should clearly explain the hardware contents of the kit and the correct set-up of the device, such as entering a code or reading the display.

Ongoing Monitoring for Compliance

While in-person monitoring will be completed during the initial sessions, subjects may be monitored and/or contacted to confirm compliance throughout the remaining sessions. Subject interaction will be maintained (e.g., through secure video) to quantify compliance (device preparation, electrode saturation/placement, stimulation protocol) with corresponding corrective steps. As an example, secure video will be scheduled and maintained with each subject daily. Visual confirmation will ensure proper set up, appropriate home environment, and acceptable impedance. Following these checks during monitoring, subjects will be given their one time use code for that session (**Figure 7**).

Ongoing Monitoring for Treatment-Emergent Adverse Effects

Before starting a session, study staff will ask the subject about any adverse events since the last session, with clearly defined stop criteria if anything is reported that is of clinical concern

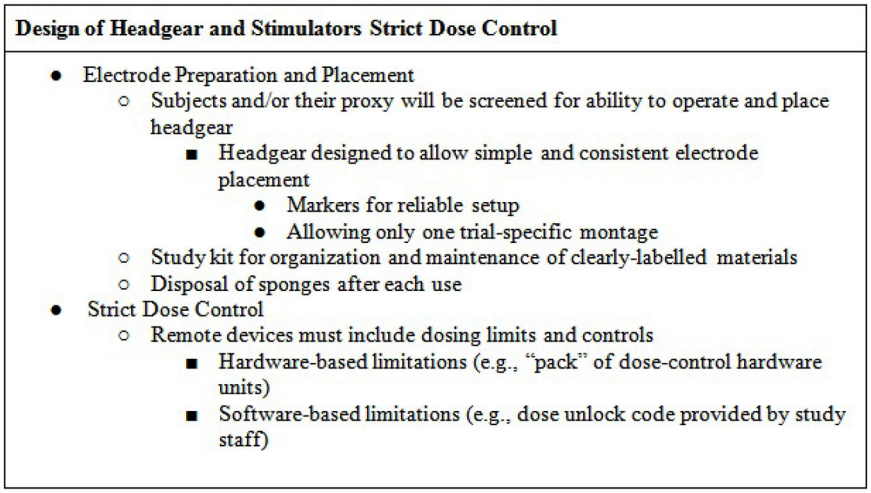

FIGURE 6 | Guidelines for study equipment.

related to safety or tolerability. In addition, subjects will be asked to report pain and/or discomfort level at set points during the stimulation. If pain crosses a given threshold, there will be an immediate stop in place in order to prevent any risk of skin burn (Loo et al., 2011) and the supervising staff will assess whether this has occurred due to suboptimal treatment technique. If tDCS causes pain above the given threshold despite adequate treatment technique, subjects will be withdrawn from the study. After the session, subjects will be again assessed by study staff for any adverse events. Subjects will also record their experience in the study-specific materials.

Guidance to Identify and Implement Discontinuation of a Session and/or Study Participation (Including Emergency Failsafe Procedures) Tailored to the Treatment Population's Level of Need

Finally, during training and in reference materials, subjects will be instructed to abort the session if they need to immediately discontinue stimulation by allowing ramp down and then removing their headset. These instructions will be used if any subject reports significant discomfort or other adverse event, otherwise needs to discontinue a session, or if study staff determines that the session should be discontinued.

Examples of Clinical Trial Applications and Population-specific Adaptations

The authors' interest in remote (non-clinic) tDCS for clinical trials has facilitated effort to develop study protocols for specific patient populations. Below, we provide examples of population-specific considerations that may navigate tailoring the guidelines described above to specific populations with differing limitations and needs. These summaries are not intended to be exhaustive but rather illustrate salient features of applying the above eight principles to specific applications. Once population specific protocols have been implemented, and the feasibility of these methods has been confirmed within the target groups, more expansive clinical trials can apply them to study the effectiveness of the treatment.

Attention Deficit Hyperactivity Disorder (ADHD)

The immediate facilitatory effects of tDCS on cognitive abilities often seen impaired in ADHD has prompted interest in whether or not the technique might have a therapeutic effect. For instance, a recent study of ADHD-diagnosed children in another experiment showed that 0.75 Hz oscillating tDCS increased EEG-recorded slow wave oscillation during sleep, and subsequent memory recall the next day (Prehn-Kristensen et al., 2014). One brief tDCS trial in non-ADHD subjects showed better response inhibition task performance after 5 consecutive days of training with concurrent 1.5 mA anodal tDCS stimulation than training alone (Ditye et al., 2012). The latter suggests that tDCS paired with cognitive training/rehabilitation techniques might have the highest potential for efficacy in minimizing ADHD-related behavioral dysfunction. However, previous trials that combine these therapeutic approaches typically last 1–3 weeks, making clinic visits impractical for a typical family that contends with school demands and extra-curricular activities, worsened when there is more than one school-aged child in the home. Any clinic-based tDCS trial for ADHD not only would be plagued by poor compliance and high dropout, but it is also likely that only the most motivated of families and subjects would complete treatment, complicating generalizability and efficacy inferences.

Remotely-supervised tDCS performed is an obvious approach to circumvent the main obstacles, but the age and behavioral characteristics of the patient population introduce unique issues to any home-based tDCS clinical trial. ADHD is a behavioral disorder whose hallmarks are distractibility, restlessness, and motivational issues--all of which must be managed effectively within a standardized tDCS delivery protocol. Although self-administered tDCS for adults diagnosed with ADHD

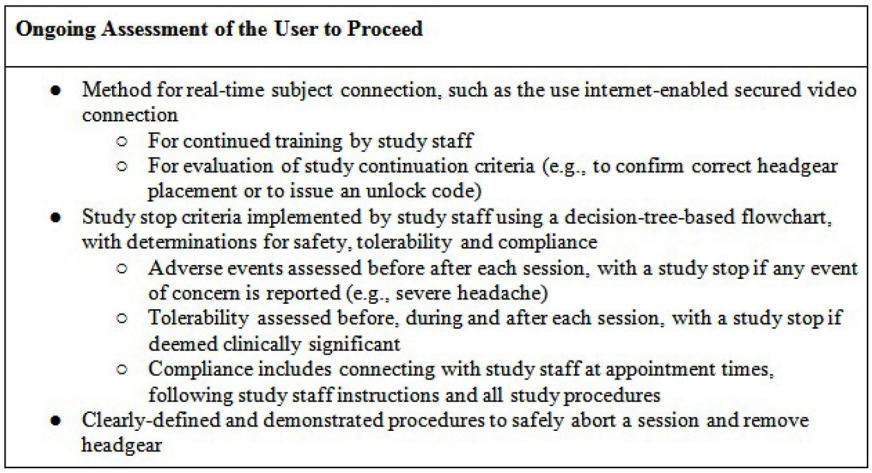

FIGURE 7 | Guidelines for ongoing assessment.

certainly is feasible, it is more likely that trials will consider tDCS with older children or adolescents, as tDCS has been shown to be safe with these age groups. However, most institutional review boards will not likely approve trial protocols where youth are asked to set up and administer tDCS themselves, suggesting effective trials must plan to overcome and troubleshoot issues arising from parent training to administer tDCS properly. Such issues include effective parent screening/training, attention to how dyadic interactions influence motivation, and special care in assessing compliance and outcome. To accommodate these special considerations, we recommend a trial design that at minimum includes: (1) a clinic visit for consent, clinical assessment, and training with particular attention paid to educating families that treatment must be a "whole family" cooperative effort, (2) an "at home" visit prior to treatment so that research staff can assess and advise tDCS equipment set up and other technical issues, (3) careful consideration of whether every tDCS session should be remotely-supervised (e.g., via video teleconferencing) to ensure optimal protocol adherence; and (4) formal consideration in trial design of how ADHD-related behavior interacts with both treatment delivery, motivation, or outcome.

Some specific recommendations for ADHD protocols include:

- *Parent preparedness, training, and motivational issues*: Informed consent for a remotely-supervised tDCS trial should emphasize the multiple types of training required for parents who will administer tDCS. At minimum, parental tDCS technical proficiency should be demonstrated as suggested above, with at least 1 clinic visit and 1 remotely-supervised session, if not at each daily session. If computer-administered cognitive training techniques will accompany tDCS stimulation, separate training should be provided in how to start, stop, and evaluate the successful implementation of such techniques. In addition, parent training should be provided in how to properly motivate their ADHD-diagnosed child. Obviously, an important goal is to avoid punitiveness or coercion that might occur if parents are more motivated than their children, but it is equally as important is to standardize and measure motivation across the trial. For example, simple behavioral contingency management techniques should be considered as standard, especially for younger age groups. Protocol-specific guidelines on how and when to provide positive reinforcements should be made explicit; their use should be quantified by trial staff weekly.
- *Dyadic interaction impact*: It is not yet known what interaction styles or personality factors might make some parents more effective in operating and supervising tDCS at home than others. Until such study has been done, we recommend that each trial should make effort to formally assess the nature of parent-child dyadic interactions or familial relationships styles to see if they moderate treatment compliance or outcome.
- *Preparation for tDCS delivery and Monitoring of Potential Treatment Barriers*: Homes with children are different than those without. For tDCS with a child or teenager, tDCS should be set up in a specially-designated quiet room and performed without distraction or interruption, preferably with the cooperation of the whole family during treatment delivery to reduce distractions. Protocols should set clear guidelines for whether or not breaks are permitted during training and set guidelines for them. A standardized compliance checklist should be used for each session, which emphasizes whether ADHD-related behaviors that could have interfered with treatment occurred and how they were managed. Any concurrently-done computer-administered cognitive training ideally will be internet-enabled. This will allow research staff to remotely verify that any exercises were set up and run correctly, as well as offers the potential for any behavioral performance data to be uploaded for secure storage at the clinic site after each treatment session.

- *Careful Choice of Outcome Measures*: Although it is likely that the primary outcome measures of any tDCS trial would be performance on tests of a specific cognitive domain, (either because it is specifically targeted by concurrent cognitive training or merely because it is one of several domains often impaired in ADHD), secondary outcome measures should include ADHD symptom severity checklists or ADHD "problem behavior" inventories (e.g., Brown ADD Scales). Because of the subjective nature of the latter types of assessments, it is important to use multiple respondents (e.g., parent and teacher). Similarly, the most effective trials will include appropriate placebo conditions in order to mitigate expectancy effects.

Depression

There is a long history of the use of "brain polarization", essentially an earlier form of tDCS often given at lower stimulus intensities, to treat depression (Arul-Anandam and Loo, 2009). Over the last decade, in the context of the emergence of brain stimulation treatments for depression (e.g., transcranial magnetic stimulation) and developments in tDCS equipment, methodology and scientific understanding, interest has rapidly emerged in tDCS as a treatment for depression. tDCS has been applied both to treatment resistant depression (i.e., in subjects who have failed to improve after treatment with antidepressant medication) and to non pharmacotherapy resistant depression, as some patients may prefer a non medication form of treatment. From 2006, evidence from several placebo-controlled, randomized clinical trials has indicated significant antidepressant effects for tDCS (Loo et al., 2012; Brunoni et al., 2013a; Shiozawa et al., 2014). A key barrier to the widespread use of tDCS for this common disorder is the requirement to travel to a treatment center for multiple sessions as repeated treatment sessions, typically given on consecutive weekdays over several weeks, are often required to optimize clinical response. For example, the Loo et al. (2012) study suggested that extension of the treatment period from three to 6 weeks resulted in greater clinical improvement. After the acute treatment course, ongoing "maintenance" tDCS, given weekly to fortnightly, has also been reported to be useful in maintaining improvement gained in the acute phase and preventing relapse of depression (Martin et al., 2013a).

Several specific issues need to be considered when applying tDCS in depression trials:

- An important precaution in this patient group is suicide risk, which may fluctuate from day to day and should be closely monitored. It is unknown if tDCS may lead to increased suicide risk early in the treatment course (as has been proposed with antidepressant medications), either due to improved motivation, or specific treatment-related effects.
- Dose-control, i.e., control of access and restriction of stimulation to pre-programmed stimulation is important as a safeguard so that the device cannot be used for deliberate self-harm.
- The research team should closely monitor fluctuations in mental state, which may impinge on the subject's ability to adequately perform the tDCS procedure at home, for example, due to changes in motivation or concentration. Thus, it is possible that a subject initially assessed as capable of performing remotely supervised tDCS at home, later becomes unable to adequately continue treatment at home—contingencies should be made for this event. Conversely, given findings that tDCS improves information processing speed in depressed patients (Loo et al., 2012) it is also possible that subjects initially assessed as not capable of performing remotely supervised tDCS at home, who may need to commence acute treatment at the treatment center, may later be able to continue the acute treatment course and ongoing maintenance treatments at home under supervision.
- As part of the initial assessment of suitability for home-based, remotely supervised tDCS, a thorough psychiatric assessment by an experienced clinician is required, evaluating not only mood, but also personality style, current stressors and social and family support. All of these factors should be considered in evaluating a person's ability to comply with tDCS procedures, likely fluctuations in mental state and risk.
- The majority of depressed patients presenting for treatment are likely to be on a combination of psychotropic medications, including antidepressants, atypical antipsychotics, anxiolytics, lithium and anticonvulsant mood stabilizers. Further, alterations in concurrent medication treatment may occur frequently common in order to manage side effects, achieve better antidepressant response or provide symptomatic relief (e.g., sleep, anxiety). As there is evidence that anticonvulsant and benzodiazepine medications may affect the efficacy of tDCS, these medications are best avoided if possible. The tDCS team should maintain close liaison with the subject's treating doctor(s) throughout the tDCS treatment course, to optimize concurrent medications and to establish procedures for clear and prompt communication about any alterations in medications.

Multiple Sclerosis (MS)

For those living with MS, treatments using tDCS have the potential to directly alleviate common yet refractory symptoms including pain, fatigue, depression, and sensory and motor dysfunction (Palm et al., 2014). An important first step is to establish the procedures for feasible at home use, with consideration of potential motor and cognitive impairments.

For this patient population, the emphasis is on extensive and ongoing screening procedures, as well as streamlined and simplified equipment design and set up. To ensure compliance, safety, and assist with training, a secure, daily video monitoring protocol should be implemented.

Further recommendations for MS protocols include the following:

- Screening is an important first step as remotely-supervised tDCS will not be appropriate for all MS patients. A treating neurologist should ensure that the subject has potential suitability for operating the headgear and device. This would include cutoffs for minimal neurological (motor) and

cognitive function. For instance, severe motor impairment can be screened for using the Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983), excluding those with scores of 6.5 or greater. In addition, subjects should be excluded from a remotely-supervised protocol if any visual, auditory, or motor deficits prevent the ability to understand the study instructions or operate the device or laptop computer (**Figures 1**, **3**). Minimal cognitive ability for participation could also be defined, for example by establishing cutoffs using the Brief International Cognitive Assessment in MS (BICAMS; Benedict et al., 2012) to exclude those with severe cognitive deficits.

- The study device should be simple to operate and engineered to unlock single tDCS sessions through a one-time use passcode. Headgear should also be simplified for use. For example, headgear should be modified with a hat-like design to ensure minimal motor requirements. In addition, device kits should be prepared and organized to ensure maximal ease in terms of sponge pocket set-up and daily materials.
- Clinical and research staff should be trained through a study technician manual on the device setup (programming sessions, retrieving session codes), headgear placement, and subject interactions (requirements for a successful session, items that qualify as "stop" criteria, and troubleshooting). In addition, research staff should be trained on how to safely abort a subject session and on procedures to reestablish video connection if lost.
- Subject training should occur during an initial in-person training session where each subject will view an instructional video, practice the technique in full and ultimately complete their first tDCS session. Beyond training, these initial visits will ensure inclusion and exclusion criteria are met. Subjects must have a suitable home environment (e.g., distraction free location and space to complete the sessions) access to internet, and the ability to commit to tDCS sessions.
- An instructional video should support training and implementation, be accessible to the subject throughout the study, and cover all details necessary to complete a session. The video should contain information on general materials, a step by step guide to set up the device, how to abort a session in case of emergency, and the means of properly ending a session and disposing of materials.
- Stop criteria (assessed at baseline, during sessions, and at follow-up) should be used as a gateway for the subject to proceed at each step (**Figure 3**). The protocol should be designed with a series of checkpoints to be met to address compliance (attendance, ability to complete the procedures as instructed, following study guidelines) and tolerability (at any time if any predefined events are reported or if pain crosses a threshold).

Palliative Care

Palliative care is an interdisciplinary model of care for patients with serious or life-threatening illnesses. The goal of palliative care is to manage symptoms of the disease and to mitigate illness burden for the patient and family from the time of diagnosis until the end of life. In the U.S., palliative care is available through both hospital-based and community-based palliative care programs (Hauser and Kramer, 2004; Defilippi and Cameron, 2010; Connell et al., 2013; Kamal et al., 2013). An overall goal of community-based palliative care is to provide adequate support in symptom management, and psychological and spiritual support to the patient and family so that the patient can remain at home, even during the terminal phase of the disease. Therefore, the development of novel home-based approaches for symptom control is highly relevant for this patient population.

Although outcomes targeted in existing tDCS studies, such as pain, mood, sleep, cognitive performance, or overall quality of life, are highly relevant for palliative care patients, there are numerous barriers of an access of palliative care patients to the tDCS studies. The burden of repeated visits to the research facility in order to receive the tDCS application has been among the major obstacles. Therefore, the development of the mini-CT tDCS enabling home-application provides an opportunity for the palliative care patients to be included in tDCS studies. However, designing study protocols of remotely-supervised tDCS for palliative care patients requires specific considerations, such as the following:

- *Involvement of family caregiver:* Palliative care subjects frequently rely on an assistance of family caregivers. Therefore, it is likely that the home-based tDCS application will be delivered by the family caregiver rather than self-performed by the subject. Thus, both the subject and the family caregiver may need to be included in the study.
- *Minimizing burden to the subject and the family caregiver*: It has to be kept in mind that both the subject and the caregiver bear the burden of the illness, and the level of their overall distress may be high. Therefore, study procedures pertaining to the tDCS procedure and data collection have to be user friendly, easy and not time-demanding. Further, time planning of study procedures should leave reasonable margins acceptable for both the dyad of subject-caregiver and the study personnel, for example when scheduling the real-time video monitoring of the procedure. Further, it needs to be taken to the account that the tDCS stimulation usually takes 15–20 min during which the subject has to remain seated or in the bed, without walking around. Therefore, subjects who for variety of reasons, such as restlessness, are not comfortably able to comply with that requirement are not good candidates for the tDCS procedure. Another aspect to consider in this category is data collection, especially in study population involving palliative care subjects at advanced stage of the illness. While data collection in healthy populations may include extensive questionnaire sets and testing, data collection in palliative care subjects should very carefully reflect the specifics of the involved population.
- *Polypharmacy*: Symptom management in palliative care frequently relies on pharmacological treatments, often including multiple medications. There is growing evidence indicating that certain agents (such as NMDA antagonists or amphetamine) may alter (inhibit or enhance) tDCS effects. This requires careful consideration when planning the tDCS protocol, because it is unlikely that medication wash-out prior

the study participation would be feasible in palliative care patients.

- *Feasibility*: Overall, the feasibility of the home-delivered remotely-monitored tDCS in palliative care patient population is multifaceted, including (but not limited to) the following elements:
- The patient's and family caregiver's understanding of the procedure, their willingness and ability to participate in the study.
- Caregiver's ability to perform tDCS specific procedures [after training]: Establishing videoconference connection; Assembling the electrodes and the head set; Positioning the headset on the subject's head; Turning on-off the tDCS unit; and the procedure has to be regarded by the involved caregiver as acceptable for him/her and the subject;
- Subject's acceptability and tolerability of the procedure: Able to remain seated or in bed for the 20-min stimulation [does not interrupt the stimulation session by walking around]; Able to provide a brief feedback or numerical rating when asked; Regards the procedure as acceptable; Tolerates the tDCS procedure (in the means of adverse events);
- Home environment: the Internet connectivity sufficient for the videoconference connection; sufficient space to accommodate the tDCS and videoconferencing devices.

Conclusion

Remotely-supervised tDCS can serve as an extension of in-clinic administered tDCS sessions. Proper frameworks around clinical staff training, user capability, training and monitoring guides are intended to maintain the same level of safety and tolerability experienced within the clinic setting. Careful consideration of each of these criteria is essential to a remotely-supervised trial. Future expansion toward a more robust training method for clinical staff on the technique will further optimize its application. In addition, following the completion of each clinical trial, population-specific modifications will be considered within the training, design, and monitoring of such patient populations. For some subjects or populations, prescription for direct home use may ultimately be the resulting clinical application, while others may be eligible only for continued remotely-supervised use. Validation of the compliance experienced in remotely-supervised tDCS trials will serve as a means of comparison to the level of compliance observed within in-clinic trials. Expanding the patient populations able to comply with a tDCS trial through remote supervision can ultimately broaden the reach of clinical trials, helping to deepen the current understanding of tDCS. With these principles in place, tDCS clinical trials will expand with results to ultimately guide appropriate and effective clinical use.

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A role for neuromorphic processors in therapeutic nervous system stimulation

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The motivations behind the development of many neuromorphic processors have been dominated by either the creation of better artificial intelligence, or novel non-von Neumann computing paradigms. A result of this impetus has been a number of low-power processors capable of simulating many different biological features of the nervous system. Power efficiency is crucial for deployed neuromorphic systems, but it also opens this technology up to other energy restricted applications. In this opinion, we suggest two such applications pertaining to therapeutic stimulation of the nervous system where closing the control loop could be assisted by advances in neuromorphic architectures: (1) deep brain stimulation (DBS) in the treatment of Parkinson's disease and (2) epidural spinal cord stimulation (ESS) for restoring voluntary motor functions. Though there are still questions that must be addressed before this would be feasible, but we are suggesting that the technological barriers—in both the algorithms and hardware—can be overcome with directed funding and research.

Neuromorphic processor research is centered around the creation of brain-like intelligence through power-efficient circuits that borrow elements directly from biology (Mead, 1989). The applications for these projects range from brain-scale simulations (Gao et al., 2012; Benjamin et al., 2014) and *in silica* experimentation (Schemmel et al., 2010; Furber et al., 2012), to brain-like computing and learning (Merolla et al., 2011; Srinivasa and Cruz-Albrecht, 2012; Cruz-Albrecht et al., 2013; Rahimi Azghadi et al., 2014; Schmuker et al., 2014). These projects promise unrivaled access to large-scale models of the brain as well as insight into the unique non-von Neumann computation that biological systems appear to achieve.

Regardless of the motivation, the tangible result of these efforts has been an accumulation of low-power circuits capable of emulating various elements of the nervous system. Although these are essential for embodying robotic systems and augmenting current super-computing paradigms, they also have the potential to assist in nervous system stimulation control. This application is outside the scope of the currently funded neuromorphic hardware projects, but with new insights and technological advances, it is one that will be particularly beneficial.

1. MODEL BASED CONTROL

In our current capacity to monitor neural circuits, most system variables are unobservable. One strategy for estimating these unknown system variables and parameters is by employing an Unscented Kalman Filter (UKF) to combine the observable and unobservable states. The UKF employs a set of known dynamical equations and observation functions with the measurable data to update an approximation of the state and its uncertainty. At each update, sigma points—system states that are consistent with the current state uncertainty—are selected and used to integrate the system. These are combined with estimated mean state values and the approximate uncertainty. A gain matrix then updates the new most likely state of the system. The schematic for this organization is illustrated in **Figure 1A**. Applying this kind of feedback control to biological systems was initially demonstrated by Voss et al. (2004) but has since been demonstrated on a number of control and estimation problems (Abarbanel et al., 2008; Li et al., 2009; Ullah and Schiff, 2009, 2010; Schiff, 2010; ODoherty et al., 2011; Aprasoff and Donchin, 2012; Schiff, 2012; Liu et al., 2014).

By using a model of the area under stimulation, both the activity and state of that area can be approximated—something that is not directly measurable. The model, constructed from the current understanding of the anatomy, can then be used to find an optimal set of stimulation parameters. In addition, the model output can be used as the feedback into a control system that can not only dynamically tune the stimulation parameters but also adapt to the physiological circuit remodeling—providing the highest possible therapeutic benefit. Embedding these models in low-power neuromorphic hardware would facilitate a transition into implantable devices.

A discussion of control inherently implies observability of the system. However, observability alone is useful to current nervous system stimulation strategies. Observing the unknown—or unreachable—states of the physical system, would provide a way to automatically tune the stimulation parameters—assisting clinicians in finding the optimal set points in open-loop control. Finally, in addition to the UKF there are other

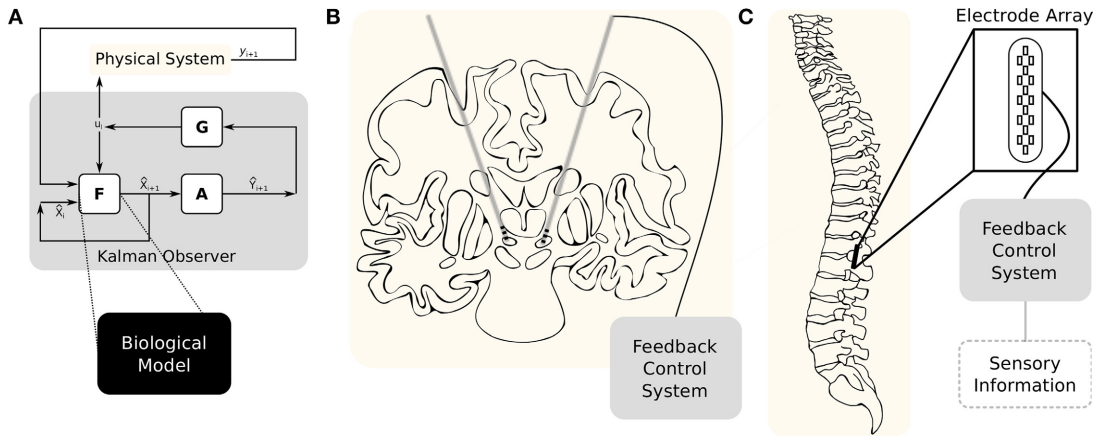

FIGURE 1 | Example therapeutic applications of model based control. **(A)** The system dynamics are described by a model, *F*, and the observations are described by a function, *A*. In most systems those observations are going to be noisy, so a covariance matrix, *R*, will account for that. After one step of *F*, using the resulting sigma points will provide $\tilde{X}_i = F(X_i)$. A new set of observations can then be found, $\tilde{Y}_i = A(X_i)$. The means over these two matrices are the *a priori* state and measurement estimates. The *a posteriori* state estimate, $\hat{x}$, is now dependent on the state estimate, $\tilde{x}$, the measurement estimate, $\tilde{y}$, the actual measurement, *y*, and the Kalman gain matrix, *G*. **(B)** Diagram of deep brain stimulation in the treatment of Parkinson's disease. Adapted from Thibeault and Srinivasa (2013). **(C)** Example epidural spinal cord stimulation for restoring voluntary motor functions.

model-based control schemes that could be employed here.

2. DEEP BRAIN STIMULATION IN THE TREATMENT OF PARKINSON'S DISEASE

The application of DBS to patients with pharmacoresistant Parkinson's disease can be traced back to the early 1980's (Montgomery Jr, 2012). In DBS, dual electrodes are implanted bilaterally into the nuclei of the basal ganglia (see **Figure 1B**)—the current target is the subthalamic nucleus. Constant electrical pulses are then injected into the electrodes. After implantation, clinicians will experiment with frequency, amplitude, and duration of those electrical pulses to find a configuration with the highest benefit. Finding that point however, is an inexact science and periodic adjustments to compensate for neural plasticity are required. Although there is a proven clinical benefit to DBS, there is no clear explanation for its mechanism of action.

Although the open-loop configuration of DBS has proven capable, closed-loop control of DBS has been shown to be a more effective treatment in both theoretical (Santaniello et al., 2011), and physiological experiments (Rosin et al., 2011). For example, in Rosin et al. (2011) a simple feedback loop was created where the activation of the DBS pulse was triggered by spiking in a reference structure—either the internal segment of the globus pallidus or primary motor cortex. The control paradigm demonstrated a larger reduction in pallidal oscillations and akinesia compared to open-loop DBS. The resulting system—although brilliantly designed—is an incredibly simple solution and one that exemplifies the therapeutic advances that can be made with adaptive feedback control systems.

The class of model-based control of DBS suggested here has already been demonstrated in simulation space by Schiff (2010) using the simple neuron implementation of Rubin and Terman (2004). Although the mathematical model used in that study was computationally cheaper than the alternative, it is still difficult to simulate in a low-power microprocessor. Aspects of the original Rubin and Terman (2004) results were implemented using a more hardware friendly model in Thibeault and Srinivasa (2013), however, the required level of abstraction in a control paradigm is still unclear. Despite unanswered questions, these studies are encouraging and demonstrate the feasibility of the strategy.

3. EPIDURAL SPINAL CORD STIMULATION

The recent discoveries in the use of epidural spinal cord stimulation—diagrammed in **Figure 1C**—on patients with motor complete paraplegia has revealed a therapeutic pathway toward restoring voluntary motor function (Harkema et al., 2011). However, the mechanisms behind this benefit as well as the supporting technology is still immature. The current state-of-the-art involves randomly tuning the stimulation parameters manually until a physiological improvement is observed—these parameters include both the duration and amplitude of the stimulus as well as anode/cathode pairings. There have been efforts to apply Bayesian optimization approaches to automating the parameter search but these did not directly account for the relevant biological structures (Desautels, 2014).

Additionally, it has been suggested that the therapeutic restoration of motor control is mechanistically dependent on the remodeling of the remaining spinal circuits (van den Brand et al., 2012). Having a control strategy as well as a model that are adaptive to the plastic changes within the spinal circuits would require less manual parameter adjustments over the life of the implant.

As a clinical treatment, ESS is still underdeveloped. However, it is one that could benefit from a model-based control strategy—either as an observer system for parametric optimization or as a complete closed-loop solution. Although the fidelity of the spinal cord model and the source of sensory feedback have not been fully explored, in many ways this appears

to be a more tractable problem compared to DBS—it may also prove to be an ideal alternative as well (Fuentes et al., 2009). The accessibility of the spinal cord as well as the simplicity of the microcircuit may make closing the loop on ESS more feasible. However, if more finely tuned control of the individual muscles is required, the complexity of the problem could quickly out pace that of DBS.

4. CONCLUSION

Despite the technological and theoretical advances outlined here, there are still obstacles to overcome. Where and what to measure when closing the loop for both DBS and ESS is not entirely clear. The stability of the hardware measuring those signals is also a concern. Furthermore, as mentioned above, the appropriate level of biological fidelity required in the model has not been fully resolved. The proposed use of neuromorphic hardware implies that the model for the control system actually requires high-fidelity. In DBS treatment of Parkinson's disease this appears to be the case. However, for spinal-cord stimulation, it may not be required. Regardless, closed-loop strategies are clearly more effective and the theoretical and technological barriers are low enough that a concerted effort should be made to advance this concept toward clinical treatments.

Finally, model-based control strategies will not only improve the therapeutic benefit but the power consumption as well. Rather than blindly applying stimulation, pulses can be applied only as needed. Utilizing neuromorphic hardware will add to that power savings by both reducing the computational burden and providing the necessary biological detail for model-based control.

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Brain-machine interfaces as a challenge to the "moment of singularity"

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Ray Kurzweil predicts that artificial intelligence will equal and then surpass human intelligence in the not-too-distant future, in what he calls the "moment of singularity." Advances in brain/machine interfacing (BMI) may be viewed as a challenge to this futuristic prediction. BMIs strive to instrument human brains with unlimited memory, calculation, and communication abilities, which provide a competitive edge to human brain power versus artificial intelligence. This paper makes a case for a hybrid human/robot that merges the brain function with artificial intelligence components, and prevents the "moment of singularity" from ever occurring.

KURZWEIL PREDICTIONS

Kurzweil has made predictions regarding computers and artificial intelligence in his four books (Kurzweil, 1992, 1999, 2005, 2012). In his 2005 book "The Singularity is Near, when Humans transcend Biology" (Kurzweil, 2005), he predicts that by the year 2045 artificial intelligence will be equal to human intelligence, an event he calls the "moment of singularity." His most recent book "How to create a Mind" (Kurzweil, 2012) brings the singularity date forward in time to 2029. He argues persuasively in that book that artificial intelligence embodied in computers will far surpass human intelligence as the 2030s roll on. He makes an excellent case throughout the text of how the brain operates as a hierarchical system and how this is important in how to create a mind.

In that book (Kurzweil, 2012), he makes a second somewhat contentious point about how the neo-cortex can be enhanced by artificial intelligence. He suggests on page 244 that using intelligent computers no bigger than a red blood cell, intelligence will be introduced into the biological brain in a minimally invasive way via the blood stream. Thus, rather than just making the case for artificial intelligence within a computer, he alludes to the scenario wherein we will enhance our present brains. However, he does not say *when* it will happen in a meaningful way. He does state that artificial intelligence will equal human intelligence by 2029 (the moment of singularity), he does not predict when intelligence will enhance biology brains. Perhaps detailing "how and when" may well be the subject of his next book.

MY OWN FUTURISTIC VIEW

This issue of "how and when" has already been proposed in my book: "2051" (Royal, 2013). This brief novelette predicts via a human story that brain machine interfacing will provide humans with a robotic shell containing the brain, and with all emotional and intellectual functions enhanced by information accessible from within the robotic shell. This human brain/robot allow the loving couple to explore the universe. The hypothesis is that enhanced brains will be incorporated into robotic machines that will *not* lose human status. Clearly, success in this venture will delay the original singularity moment of 2045, though perhaps not Kurzweil's revised date of 2029. No mention is made in my novel of the 2029 date, being unknown at the time of writing in 2006 and 2007 (Royal, 2013). (Full disclosure: This writer published "2051" under a pseudonym, Alpha O. Royal).

BRAIN-MACHINE INTERFACES

Interestingly, many members of the brain-machine/computer interfacing research community believe that BMIs may have a key role in the advancement of intelligence that constitutes the core of Ray Kurzweil's hypotheses. The challenge is to delay or perhaps completely abort his prediction. This could be achieved by enhancing the human brain so that we stay one step ahead of intelligent computers. Think: If it were possible to provide humans with instant and total memory, access to all information, infinite calculation ability and instant communication with whomever, whenever and wherever, we could have intelligence that would be superior to any present day intelligence that a computer has today (Li et al., 2012). Enhanced memory and knowledge can provide an individual with an unparalleled asset and make you superior to all other humans except those others who have this asset. Having all calculation abilities and instant communication would complete the superior human being (Fitzsimmons et al., 2007; O'Doherty et al., 2011). But would we be superior to Kurzweil's predicted intelligent computers? Is it possible that before 2045, the original year of singularity, or 2029, we humans could have superior intelligence and thus delay or abort Kurzweil's prediction?

THE ALTERNATIVE HYPOTHESIS

The hypothesis in "2051" is based on our present technology and where it is likely heading. For example, if recording and stimulating electrodes continue on their present developmental path, it is likely that the brain can be instrumented completely (Marblestone et al., 2013). Recording and stimulating electrodes would be placed over the hemispheric cortices primarily, and also within deeper structures such as the basal ganglia as is done today for Parkinson's disease (Marblestone et al., 2013). These recording and stimulating electrodes would provide all essential inputs and outputs.

ISSUES WITH THIS HYPOTHESIS

A very important problem is immediately raised however: How can the instrumented brain assimilate all the information that would descend on it? How could we restrict and channel it to avoid being overwhelmed with useless information (Fitzsimmons et al., 2007; O'Doherty et al., 2011)? In these papers, monkeys received artificial sensations via intracortical stimulation. Initially, the brain was overwhelmed and the animals did not understand the meaning of this input. However, later they started to make sense of the artificial sensation, that is they developed a new sense. They then learned new discrimination tasks faster. Carefully placed inputs would help. For instance, visual input would travel from artificial eyes to the electrodes in the visual cortex, and auditory input would travel to the auditory cortex, and so on (Fagg et al., 2007; Bensmaia and Miller, 2014). But when downloading information does it consciously or subconsciously arrive at visual or auditory cortex? Would it be better if the information goes directly to the hippocampus, originally thought to be the "gateway to memory," or to other sites? If through the hippocampus, is the information available to consciousness or is it only conscious and available on demand when needed? If that is how it is to occur, then why would the information not overload memory storage in the brain? How would our biological brain be capable of storing all knowledge? A more likely storage alternative is that all knowledge would be stored in attached computers or "in the cloud" to be available when needed (Li et al., 2012). As Kurzweil predicts, all the information is to be available within the cloud (Kurzweil, 2012). If the cloud is the modus operandi, then how would we access the information? Perhaps the same way we search and access information using Google or other search engines. These are the type of problems that we cannot answer with our present stage of knowledge of the brain. These issues are the important ones. Only by understanding the neurophysiology of the brain more fully, can we approach an answer to these questions.

OTHER CHALLENGES

Other challenges include how the instrumented brain will interact with the body? How will it comport with the body? If the brain is thoroughly instrumented with electrodes does it even need the body? After all, the body will age and become diseased with the usual cancer, cardiovascular, or other problems. A solution is to replace the aging or diseased body and support the brain by other means (provided of course the brain itself is not diseased). Basically, all the brain requires to remain functional is a blood and cerebrospinal fluid supply that provides oxygen and nutrients, and removes metabolic products, while inputs and outputs are provided by instrumenting the brain. Thus, metabolic requirements could be provided, not by our natural bodies, but by artificial means such as miniature heart/lung/nutrient machines or internal factories. Nanotechnology is needed to provide miniaturization of hardware components in such a device and will require external replenishment of supplies from time to time or an indwelling biological factory to provide these essential ingredients.

HYBRID/HUMAN ROBOT

If an artificial heart/lung/nutrient factory were to be feasible, then why would we need a body? Well, we wouldn't. There would be no need for a biological body to provide mobility. Mobility and other functions could be maintained by a robotic shell that contains the heart/lung/nutrient factory that are all controlled by the instrumented brain. Advances with robotic hardware, software, and nanotechnology make such a development a strong possibility. It appears likely that we could end up with a *hybrid robot containing an instrumented human biological brain that controls the robotic body* (see **Figure 1**). This is a different outcome than Kurzweil's prediction of artificial intelligence in a computer, or humans with enhanced brains that have received artificial intelligence via red blood cells.

Clearly, there is a big problem with this scenario. That is, how to maintain a supply of human brains? If all the bodies are gone, where do the ova and sperm come

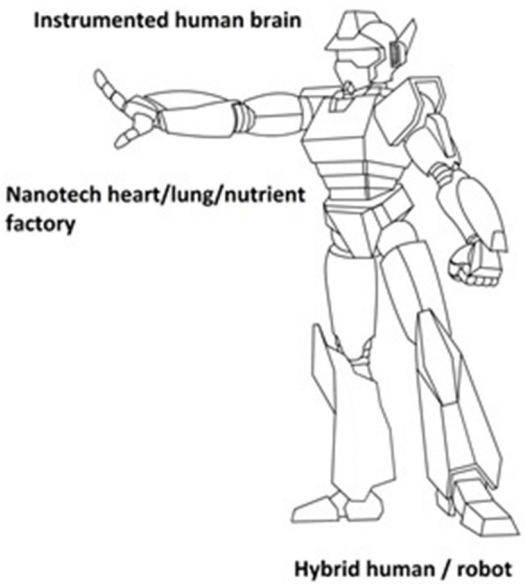

FIGURE 1 | Theoretical hybrid human / robot.

from to create more humans with brains? Banked sperm and ova are a possibility. They would be fertilized as needed and developed into humans by baby factories. Ugh! Without a supply of human brains the robots would take over completely. In that scenario, Kurzweil's prediction will only be delayed as long as there are human brains available. Once the human brains have all died off, Kurzweil's prediction will come true. *Oh darn, you think, he's right again.* Ah, but wait, tissue can be regrown. Perhaps a new human body and brain can be regrown completely and maintained, if not young, at least virile (Monaghan and Maden, 2013; Racine et al., 2014). In that case, human reproduction can take place in a biological fashion, without baby factories, thus maintaining the supply of human brains.

THE ETHICAL ISSUES

Then there are the ethical issues (Albrecht and Devlieger, 1999; Amundson, 2010; Glannon, 2014). If (a) enhanced humans, (b) computers with artificial intelligence or (c) hybrid human/robots, are fully realized, then these beings would be superior to all others who are not yet enhanced. Clearly, this would create a group of superior beings that governments would want for their own use as part of their defense/offense capabilities to protect against international aggression and threats. These hybrids could be also used as national police. This bears on the very serious issue of control of the native population, a control issue that is becoming ever more prevalent these years. The present ability to know what humans think and do through access to their communications has provided governments with knowledge that could lead to total domination of the native population. Such domination could, and likely would, be enforced by the hybrid human/robots. I raise this issue because scientific knowledge and technological achievements do not occur in a vacuum. They always have societal implications and no implication is more serious than this potential technology. *Over half a century ago*, President Eisenhower warned about these dangers in his farewell speech to the nation 3 days before he left office in 1960 as shown in a news reel of his address (Webster, 2014). Of course he made no specific mention of the technological advances that are occurring today. He discussed his fear that the military/industrial complex would become "the whole dog rather than just the teeth." The answer to this ethical dilemma is simply that the hybrid human/robot should be available to all people and not restricted to any one group, whether it be government or otherwise.

CONCLUSIONS

So the serious challenges for the brain computer interface community are not just technical, they are ethical as well. Perhaps we should not go there, but technology always takes on a momentum of its own in its inevitable and unrelenting march forwards. We cannot flee the challenge of delaying or avoiding Kurzweil's prediction. We must embrace it. That is our responsibility. But let's tread lightly and very, very carefully.

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What will this do to me and my brain? Ethical issues in brain-to-brain interfacing

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Recent brain-to-brain interfacing studies provide proof of principle for the feasibility of various forms of direct information transfer between two brains, and may lead to the development of new approaches involving memory, emotions, or senses. What makes brain-to-brain interfaces unique is the transfer of information representing specific messages directly from one brain to another, without involving any activity of the peripheral nervous system or senses. The article discusses ethical issues that arise in neural interfacing. The focus is on the implications that brain-to-brain interfaces may have on the individual at the recipient side.

Keywords: ethics, brain-to-brain interfaces, research ethics, cross species experiments, agency, personal identity

INTRODUCTION

For several years now, brain-computer interfaces (BCIs) in which brain signals are used to navigate a computer, a prostheses or a technical device, have been developed in various experimental contexts (Wolpaw and Wolpaw, 2012; Grübler and Hildt, 2014). Researchers have recently taken the next step and run experiments based on connections between two brains. These so-called brain-to-brain interfaces (abbreviation: BBIs or BTBIs) involve not only a BCI component deriving information from a brain and sending it to a computer, but also a computer-brain interface (CBI) component delivering information to another brain. What results is technology-mediated brain-to-brain communication (B2B communication), i.e., direct communication between two brains that does not involve any activity of the peripheral nervous system. In what follows, ethical issues that arise in neural interfacing will be discussed after a short introduction to recent BBI experiments. In this, the focus will be on the implications BBIs may have on the individual at the CBI side of the BBI, i.e., on the recipient.

RECENT EXPERIMENTS

In their experiments involving a non-invasive BBI, Yoo et al. (2013) established functional links between the brain of a human volunteer and the brain of a rat. The human participant initiated an intention for intervention that was then transferred to an anesthetized rat's brain. This intention stimulated the motor area responsible for tail movement and led to involuntary tail movement. Technically, the experiment combined a BCI relying on EEG-based steady-state visual evoked potential and a CBI using transcranial focused ultrasound (FUS). FUS-based non-invasive neuromodulation of the rat brain was triggered by a computer when the human participant voluntarily started a thought process representing the intention to stimulate the rat brain. The intention was initiated by the participant looking at a strobe light flickering on a computer screen. In case of high synchronization, the FUS was triggered to transcranially modulate the anesthetized rat brain's motor cortex. Thus, the human subject was able to initiate (and thus control) the rat's tail movement via the BBI mediated "on–off" trigger.

In a similar experiment, Pais-Vieira et al. (2013) used a BBI to transfer behaviorally meaningful sensorimotor information from the brain of one rat (the "encoder" rat) to the brain of another rat (the "decoder" rat). In the study, while the encoder rat accomplished a sensorimotor task requiring the selection from two stimuli, cortical activity was recorded and transferred directly to the decoder rat's corresponding cortical areas via intracortical microstimulation. The sensorimotor information transferred via the BBI guided the decoder rat to learn similar behavioral choices, i.e., based solely on the neural patterns originating from the encoder rat. Furthermore, when the decoder animal's task performance was fed back to the encoder animal, continuous BBI operation influenced the encoder rat's neural activity and behavior. Overall, the BBI provided a "direct channel for behavioral information exchange" between two interconnected brains that allowed real-time sharing of sensorimotor information (Pais-Vieira et al., 2013, p. 6). The authors go on to state that these results "indicate that animal brain dyads or even brain networks could allow animal groups to synchronize their behaviors following neuronal-based cues." (Pais-Vieira et al., 2013, p. 6).

A related study not based on BBIs but involving a similar donor/recipient design, was done by Deadwyler et al. (2013). Via a mathematical model they derived information encoding patterns from the hippocampus of "donor" rats well trained in a specified paradigm and delivered the information via electrical stimulation to "recipient" rats that had never before been exposed to the specific character of this task. The transfer of the model-derived hippocampal firing pattern from the trained donor animals to

naïve recipient animals via stimulation facilitated the recipient animals' task performance. As there was a time delay in between the encoding phase of the task and the behavioral response in the recipient animal, the study shows the transfer of a memory code, quite in contrast to the BBI-based study by Pais-Vieira et al. (2013) which relies on the immediate induction of a motor response.

Recently, Grau et al. (2014) provided the first example of conscious transmission of information between humans via a non-invasive BBI based on a BCI using motor imagery-controlled electroencephalography and a CBI that used transcranial magnetic stimulation (TMS) to induce the conscious perception of phosphenes, i.e., the experience of seeing light. The receiver subjects on the CBI side of the BBI were able to decipher the transmitted phosphene sequences carrying encrypted messages that coded for words such as hola" or "ciao."

Furthermore, there are speculations concerning possible future bidirectional BBI applications. For example, Yoo et al. (2013, p. 7) assume that "if both BCI and CBI are implemented between two awake human subjects, the information flow could be made bidirectional and communicative between apperceptive identities/individuals."

Possible future applications beyond the laboratory that have been envisioned include the use of BBIs in the military or in other professional contexts where they may allow for silent commands or may serve to synchronize behavior of a larger group of individuals. Further, applications may be seen in computer gaming, in enhancing human sensory capacities or in providing support to individuals with severe motor impairments (cf. Trimper et al., 2014).

NEED FOR ETHICAL REFLECTION

The recent studies provide proof of principle for the feasibility of various forms of direct information transfer between two brains, and may lead to the development of new approaches involving memory, emotions or senses. In view of these seminal publications on BBIs allowing information transfer between animals, between humans, and between animals and humans, there is a clear need for thorough ethical reflection.

BBIs combine the recording of brain signals on the side of the sender and brain stimulation on the side of the recipient. Each of these strategies raises a broad spectrum of ethical issues that are currently being discussed in contexts such as brain-computer interfaces, deep brain stimulation, or intrasurgical brain stimulation (Freudenstein et al., 2005; Grübler and Hildt, 2014; Unterrainer and Oduncu, 2015). What makes BBIs unique, however, is the transfer of information representing specific messages directly from one brain to another, without involving any activity of the peripheral nervous system or senses. On the side of the recipient, BBIs involve a form of information input not seen so far. Furthermore, whereas the specific "meaning" of the transferred signal is clearly defined by the technical system, the behavioral implications may be far from clear.

As BBI technology currently is in the very first stages of basic research, the ethical aspects raised in this contribution are speculative to a considerable degree. Nevertheless, it is important to reflect on these issues right now. The results will be of relevance to the design of possible future BBI studies involving human subjects and will give an idea of the broader implications and possible future uses of the BBI technology.

SOME GENERAL ASPECTS

But what exactly are the ethical issues possibly arising in brain-to-brain interfaces?

First of all, as in any kind of research involving human subjects, health-related safety issues have to be taken into consideration. In invasive systems that require surgery, there are risks concerning brain lesions. Furthermore, both in invasive and in non-invasive systems, some more indirect effects may arise: the recurring activation of specified pathways or brain regions both on the BCI part and the CBI part may influence brain functioning in various aspects.

In BBI use issues regarding agency, responsibility and liability undoubtedly will play a role (O'Brolchain and Gordijn, 2014; Vlek et al., 2014). Whereas traditional legal regulations concerning responsibility and liability in technology use may be applicable to BCIs, as suggested by several authors (Tamburrini, 2009; Clausen, 2011; Grübler, 2011), the fact that in BBIs two persons are involved complicates things considerably. The concept of "shared control" (Tamburrini, 2009), stating that in BCI use the user and the technical system together share control in achieving the output signal, undoubtedly applies to BBIs as well. Unlike in BCIs, however, there is not one person involved, but two, both of them not fully aware of their exact respective role in the system (cf. Vlek et al., 2014). Any ascription of responsibility for the outcome of any activity involving BBI functioning will be complicated by the BBI characteristic that the encoder may have initiated or significantly influenced a behavior or some sort of activity the decoder is performing (Trimper et al., 2014). Who is responsible for the consequences of activities in which BBIs are involved? The sender, i.e., the person involved in the BCI part? The recipient? The experimenter? The technical device? It may be speculated whether a concept of "hybrid agencies" (Suchman, 2007) involving several human actors might be applicable to BBIs.

Being part of a brain–brain dyad or a multi-brain system may also have complex repercussions on a person's concept of self, and raises questions concerning self-perception, individuality and body ownership (Hildt, 2011). For example, as an encoder, what is it like to be aware of another person exerting some behavior initiated or influenced by oneself? Will it be possible to clearly separate one's concept of self and the other?

Furthermore, complex problems with regard to privacy may arise, especially when the BCI component uses signals the sender is not aware of or signals the sender cannot control (Tamburrini, 2009; Trimper et al., 2014). Thus, it will be crucial to clearly define and explicitly state what kind of information will be transferred and to provide the sender with adequate measures to control the information transfer process. The same holds for the recipient in order to avoid the unconsented intrusion of information.

IMPLICATIONS FOR THE RECIPIENT

Imagine a BBI that transmits information that serves to mechanically make the decoder slightly move his left forefinger, in a method similar to the experiments run by Yoo et al. (2013) where BBI activity resulted in an anesthetized rat moving its tail. The

recipient probably realizes that something is going on (his finger is moving in an automatic manner) and—being aware of the BBI and its usual function—will deduce that some information is being transferred. Thus, he probably will not ascribe authorship to himself for this movement. However, the situation will be different if the recipient is able to actively control the outcome of the information transfer, i.e., to actively control whether or not a certain movement finally occurs. For example, a person may be able to suppress the movement in question, or the BBI may solely confer a signal that serves as a stimulus for further action.

Now imagine a more flexible BBI in which various different patterns are enacted that elicit different types of reactions in the recipient. In case of five to ten different movement patterns conveyed via the BBI, would the recipient still be sure whether it is himself or the BBI that is initiating or controlling the movements? I have doubts. This uncertainty may lead him to erroneously ascribe authorship to himself for these movements (cf. Wegner, 2002; Vlek et al., 2014).

The same holds true, with even more complex implications, in cases where a BBI was able to elicit different types of emotions or memories. In a hypothetical situation where a BBI transmits a memory code that makes the recipient recall seeing a blue ball, the recipient may be clearly aware of the fact that his recurrent recalling of a blue ball may result from a BBI whose sole function is to elicit this urge. With a higher number of different stimulation patterns available, this connection will vanish so that it will be increasingly difficult for the recipient to know whether it is he or the BBI who induces a certain movement, emotion or memory. Furthermore, the transfer of emotions will considerably influence the recipient's overall well-being.

For example, in a scenario of memory transfer in humans, similar to the experiment in rats carried out by Deadwyler et al. (2013), the recipient would end up having two types of memories: his own genuine memories and the quasi-memories[1] transferred via the BBI technology. However, he would not be able to distinguish between his own genuine memories and the quasi-memories. As for quasi-memories, the same problems arise for quasi-olfactory experiences or for quasi-emotions elicited in the context of BBI use. The recipient would no longer know for certain which of his memories, sensory experiences or emotions are genuine and which are his quasi-memories, quasi-sensations or quasi-emotions resulting from BBI information transfer. In view of this, the recipient's sense of identity would be highly questioned [cf. the philosophical debate run by Shoemaker (1970), Williams (1976), Parfit (1984), and others].

In contrast, no direct identity issues arise in the conscious information transfer described by Grau et al. (2014). In their BBI experiment, the CBI elicits phosphenes in the recipient that code for specific words. The recipient is aware of the information transfer process which involves active deciphering.

NEURAL INTERFACING, NEURAL GRAFTING, AND CROSS SPECIES EXPERIMENTS

It is worthwhile to compare neural interfacing with the ethical issues raised by other biomedical approaches. In particular, neural tissue transplantation is of interest here since the strategies of neural interfacing and neural grafting both involve the possibility of additional content being transferred to a brain.

Neural tissue transplantation studies in Parkinson's disease patients were run mainly in the 1980s and 1990s. They aimed at replacing loss of dopaminergic neurons in the brains of Parkinson's disease patients by transplanting mesencephalic tissue from the developing brain of aborted human embryos and fetuses into the patient's brain (Barker et al., 2013).

In the context of these clinical grafting trials, guidelines were developed that addressed ethical issues in the retrieval and use of human embryonic and fetal material. Some of them, among other aspects, contain a paragraph that serves to exclude the possibility of "personality transfer" or any risk of transfer of individual characteristics from the brain tissue donor to the recipient (British Medical Association, 1988; Dickson, 1989; Boer, 1994). For example, the "NECTAR ethical guidelines for the retrieval and use of human embryonic or fetal donor tissue for experimental and clinical neurotransplantation and research" developed by the Network of European CNS Transplantation And Restoration (NECTAR), say in point 7: "Nervous tissue may be used for transplantation as suspended cell preparations or tissue fragments" (Boer, 1994, p. 3). Allowing only cell preparations or tissue fragments to be transplanted serves to avoid the transfer of any of the donor's individual characteristics to the graft recipient.

Even if for practical reasons a "personality transfer" or the transfer of individual characteristics is very unlikely to occur in brain tissue transplantations, the guidelines considered this concern by having a paragraph that explicitly rules out this possibility in clinical transplantation studies. BBIs, however, directly involve the very issue that these guidelines attempt to avoid in the case of clinical neural tissue transplantation: the transfer of individual characteristics from a donor to a recipient, such as for example in the transfer of a memory code. Whereas in neural grafting a material substrate, i.e., brain tissue, is transferred, in BBIs there is a direct transfer of information from one brain to another. What matters from an ethical point of view is the same in both approaches. The possibility of transfer of individual characteristics. This discrepancy points to a clear need for further reflection on the ethical issues involved in the transfer of information in BBIs involving humans.

Cross species neural interfacing experiments also raise tricky ethical issues (cf. Trimper et al., 2014). With regard to research involving animals containing human material (ACHM), some ethical reflection currently is going on. For example, the government-commissioned report "Animals Containing Human Material" from the UK Academy of Medical Sciences (2011) identifies a category (Category 2) of ethically sensitive research involving ACHM which should be approached with caution but

[1]The term "quasi-memory" has been coined by the American philosopher Sydney Shoemaker. He describes "quasi-memory knowledge" as "a kind of knowledge of past events such that someone's having this sort of knowledge of an event does involve there being a correspondence between his present cognitive state and a past cognitive and sensory state that was of the event, but such that this correspondence, although otherwise just like that which exists in memory, does not necessarily involve that past state's having been a state of the very same person who subsequently has the knowledge." (Shoemaker, 1970, p. 271).

could go ahead if approval by a specialist committee on a case-by-case basis is obtained (cf. Abbott, 2011). Among others, this category includes research that involves the modification of animal brains, other than non-human primates, "that may make the brain function potentially more 'human-like"' (Academy of Medical Sciences, 2011, p. 110).

The introduction of more "human-like" function into an animal brain via BBIs is not totally out of reach. A possible example is the BBI-induced transfer of the ability to distinguish between different words or commands (such as left, right, up, down) and to behave accordingly. Thus, some of the considerations of animals containing human material may apply to BBI technologies as well. Furthermore, in BBIs, information transfer may also emanate from an animal to a human being. For example, (Trimper et al., 2014, p. 2) speculate on possible future interspecies BBI uses such as enhancing human sensory systems or "aiding in search-and-rescue operations, linking our brains with those of the search-and-rescue animal. " In analogy to the point raised above with regard to animals containing human material (ACHM), there is a clear need for further reflection on the ethical issues involved in attempts to modify the brains of humans in ways that might result in some "animal-like" functions.

CONCLUSION

Current BBI research opens up fascinating new communication pathways but also raises considerable practical and ethical questions. One of the central questions is whether there actually is a need for direct brain-to-brain communication. At least at the moment, it seems doubtful whether there are broader applications for such a complex, rigid and expensive technology. Furthermore, in view of the complex ethical implications arising in the BBI recipient described above, the spectrum of possible ethically acceptable BBIs seems rather limited.

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Donor/recipient enhancement of memory in rat hippocampus

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The critical role of the mammalian hippocampus in the formation, translation and retrieval of memory has been documented over many decades. There are many theories of how the hippocampus operates to encode events and a precise mechanism was recently identified in rats performing a short-term memory task which demonstrated that successful information encoding was promoted via specific patterns of activity generated within ensembles of hippocampal neurons. In the study presented here, these "representations" were extracted via a customized non-linear multi-input multi-output (MIMO) mathematical model which allowed prediction of successful performance on specific trials within the testing session. A unique feature of this characterization was demonstrated when successful information encoding patterns were derived online from well-trained "*donor*" animals during difficult long-delay trials and delivered via online electrical stimulation to synchronously tested naïve "*recipient*" animals never before exposed to the delay feature of the task. By transferring such model-derived trained (*donor)* animal hippocampal firing patterns via stimulation to coupled naïve *recipient* animals, their task performance was facilitated in a direct "*donor-recipient*" manner. This provides the basis for utilizing extracted appropriate neural information from one brain to induce, recover, or enhance memory related processing in the brain of another subject.

Keywords: memory-transfer, rodent, ensemble, non-linear model, electrical stimulation

INTRODUCTION

To understand the neural basis of memory, several features of the context in which the memories occur and are utilized, and the functional aspects of the brain areas involved, need to be identified and controlled (Hampson et al., 2008; Eichenbaum and Fortin, 2009). In prior studies we achieved both of these important contingencies as well as (1) overcoming possible alternative interpretations of the relationship between recorded hippocampal ensemble activity and the behavioral task in which short-term memory formation is necessary (Deadwyler and Hampson, 2006; Deadwyler et al., 2007), and (2) developing an effective mathematical/operational model for online prediction of CA1 hippocampal cell activity from simultaneously recorded input firing patterns from synaptically connected CA3 neurons (Song et al., 2009; Berger et al., 2011; Hampson et al., 2011). The combination of these approaches was made possible by the chronic recording of neural firing patterns in the above two major hippocampal subfields via specially designed mutineuron recording arrays that allowed simultaneous detection and analysis of behaviorally critical ensemble discharge patterns (Deadwyler and Hampson, 1997; Hampson et al., 1999, 2008). It has been shown that a non-linear multi-input/multi-output (MIMO) mathematical model provides the mean to translate the above ensemble activity into a format that allows predictions of CA1 firing patterns from CA3 activity required for successful task performance (Marmarelis, 2004; Zanos et al., 2008; Song et al., 2009).

In the following paper we demonstrate a critically important feature of the online extracted firing patterns of hippocampal ensembles by showing how alteration and facilitation of hippocampal function can be employed via direct connection with the same structure in a different "*donor*" animal performing the same task at the same time. A recent study (Pais-Viera et al., 2013) reported similar brain-to-brain transfer by directly stimulating motor cortex in the brain of a recipient rodent from a different animal. However, we report here the discovery that appropriate neural firing patterns which encode useable *memory* can be derived online from trained animals, and inserted via electrical stimulation of those same hippocampal regions to animals untrained to perform the memory extended requirement of the delayed-non-match-to-sample (DNMS) task. These findings confirm the functional significance of a previously identified "hippocampal prosthesis" (Berger et al., 2011) shown to repair and/or enhance damaged or disrupted memory processes in the same animal. However, the outcomes of the study described here also indicate ways of using brain systems from non-impaired subjects to impart functional information when and where it did not get formulated in affected subjects, via a *donor-recipient* paradigm.

METHODS

INFORMATION ENCODING BY HIPPOCAMPAL NEURAL ENSEMBLES DURING PERFORMANCE OF A DELAYED-NON-MATCH-TO-SAMPLE (DNMS) MEMORY TASK

Recording and analysis of hippocampal mutineuron activity over a number of years in rodents performing a DNMS memory task (cf. Hampson et al., 2008, 2011) provided the basis for application of a non-linear MIMO model to hippocampal neural ensemble firing patterns in the first demonstration of a memory prostheses in rodent brain (Berger et al., 2011; Hampson et al., 2012a,b). This extensively studied DNMS task requires rats to retain the position of a "Sample" lever that is presented and responded to (i.e., sample response: SR) at the start of the trial, over a temporal delay interval of variable duration (1–30 s) in order to make a "Non-match" response (NR) on the lever in the opposite position when both levers are presented simultaneously at the end of the delay (**Figure 1A**). During the delay period a nosepoke into a photocell on the wall opposite the levers is required to proceed to the Non-match phase. If there is no delay a single nosepoke produces both levers, for delays of increased duration a single nose poke is still the only requirement but animals make multiple nosepokes until the light terminates above the photocell as an indicator of delay termination and both levers are presented on the opposite wall (**Figure 1A**). **Figure 1D** (control) shows that DNMS performance accuracy decreases linearly as a direct function of the duration of the interposed delay interval.

NON-LINEAR MULTI-INPUT MULTI-OUTPUT (MIMO) MODEL DETECTION AND PREDICTION OF HIPPOCAMPAL ENSEMBLE MEMORY CODES

Electrophysiological recording during the DNMS task employs custom designed arrays of microwire (20 μm) electrodes implanted bilaterally in the hippocampus in each hemisphere to provide single neuron firing data from 8 pairs of aligned CA3-CA1 probes arranged at 200 μm intervals along the longitudinal axis in the dorsal hippocampus in rodent brain (**Figure 1B**). The neural correlates obtained from studies with these techniques in the DNMS task have been utilized in more than 2000 animals with respect to type and amount of behavioral training required for maximal performance in conjunction with extraction of distinct patterns of neural ensemble activity correlated with successful performance (Deadwyler and Hampson, 2006; Hampson et al., 2008, 2011). In recent studies the trial-by-trial nature of changes in ensemble firing patterns has been described in relation to non-linear fluctuations associated with successful task performance (**Figure 1C**), as well as applying the same non-linear model for reversing detrimental actions of drugs on performance (Song et al., 2009; Berger et al., 2011; Marmarelis et al., 2013).

This very precise MIMO non-linear mathematical model (**Figure 1C**) was employed to determine the "strength" of ensemble SR firing patterns or "codes" formulated specifically on successful (strong code) or error (weak code) DNMS trials (**Figures 1C,D**) across all delay durations. The application of this model (see *Supporting Material*) allowed prediction of CA1 neuron firing "output" patterns based on the "input" to the model (CA3 neuron firing) using Laguerre expansions of Volterra Kernels to determine the temporal relationships between spike occurrences recorded in these two areas during the task (Song et al., 2009, 2013; Berger et al., 2012). As shown previously the inputs to the MIMO model were CA3 cell discharges associated exclusively with outputs from simultaneously recorded postsynaptic CA1 cells connected via Schaeffer collateral monosynaptic connections (Witter and Amaral, 2004). Hence, as shown at the lower right in **Figure 1C**, the MIMO model analysis of CA3 and CA1 spike occurrences associated with critical DNMS task events provided the basis for online "detection" (CA3) and "prediction" of CA1 firing patterns associated with successful (strong code) vs. error (weak code) trials (Berger et al., 2011; Hampson et al., 2011). As a final verification that the MIMO model output could predict behaviorally relevant hippocampal encoded information, online calculations were utilized in a closed loop paradigm in which the detection of strong SR codes (**Figure 1C**) was used to adjust the difficulty of the same trial via increased or decreased delay duration. In accordance with the strength of SR codes (**Figure 1D**) performance was either above or below that on trials in which such SR codes were not present (Hampson et al., 2012a,b). This closed loop procedure served as the basis for the next phase in which strong SR code patterns were detected, mimicked and then administered as electrical stimulation, which is described next.

EXTERNAL INSERTION OF MIMO DERIVED FIRING PATTERNS VIA ELECTRICAL STIMULATION OF HIPPOCAMPAL CA1 NEURONS

The above successful application of the MIMO model provided the unique basis for activating CA1 cells if model derived inputs from CA3 neurons were no longer operative (Berger et al., 2011). This was accomplished by transforming the CA1 cell output pattern of the MIMO model into trains of electrical stimulation pulses (1.0 ms biphasic 20–100 μA) and delivering them in real time to the same CA1 electrode locations in the recording arrays via a multichannel stimulator (**Figure 2A**). CA1 stimulation patterns were therefore similar to the strong code SR firing patterns derived from each animal by the MIMO model from the same CA1 electrodes. Stimulation was delivered online via the inputs detected from CA3 electrodes on the same hippocampal array as shown in **Figure 2A** for hippocampal implants in both hemispheres. Intensities of stimulus pulses (20–100 μA) delivered to CA1 were adjusted to provide indications of extracellular current flow (i.e., local field potentials) at adjacent CA1 electrode locations on the same array (see below). MIMO generated strong code CA1 SR stimulation pulse trains were of 3.0 s duration and delivered within 50 ms of the detection of corresponding input patterns recorded in CA3 (see *Supporting Material*). Since both the pattern and time of application of the strong code CA1 SR stimulation were related directly to the MIMO model detection of corresponding CA3 input firing, it was also possible to deliver CA1 SR stimulation on trials in which "strong code" input patterns were not detected in CA3 recordings. This provided the means to facilitate performance above control levels by delivering strong code CA1 SR stimulation on trials that normally did not generate strong codes in CA3 or CA1 naturally (Berger et al., 2011; Hampson et al., 2012a,b).

The effectiveness of SR CA1 stimulation patterns is shown in **Figures 2B,C** as marked increases in DNMS task performance

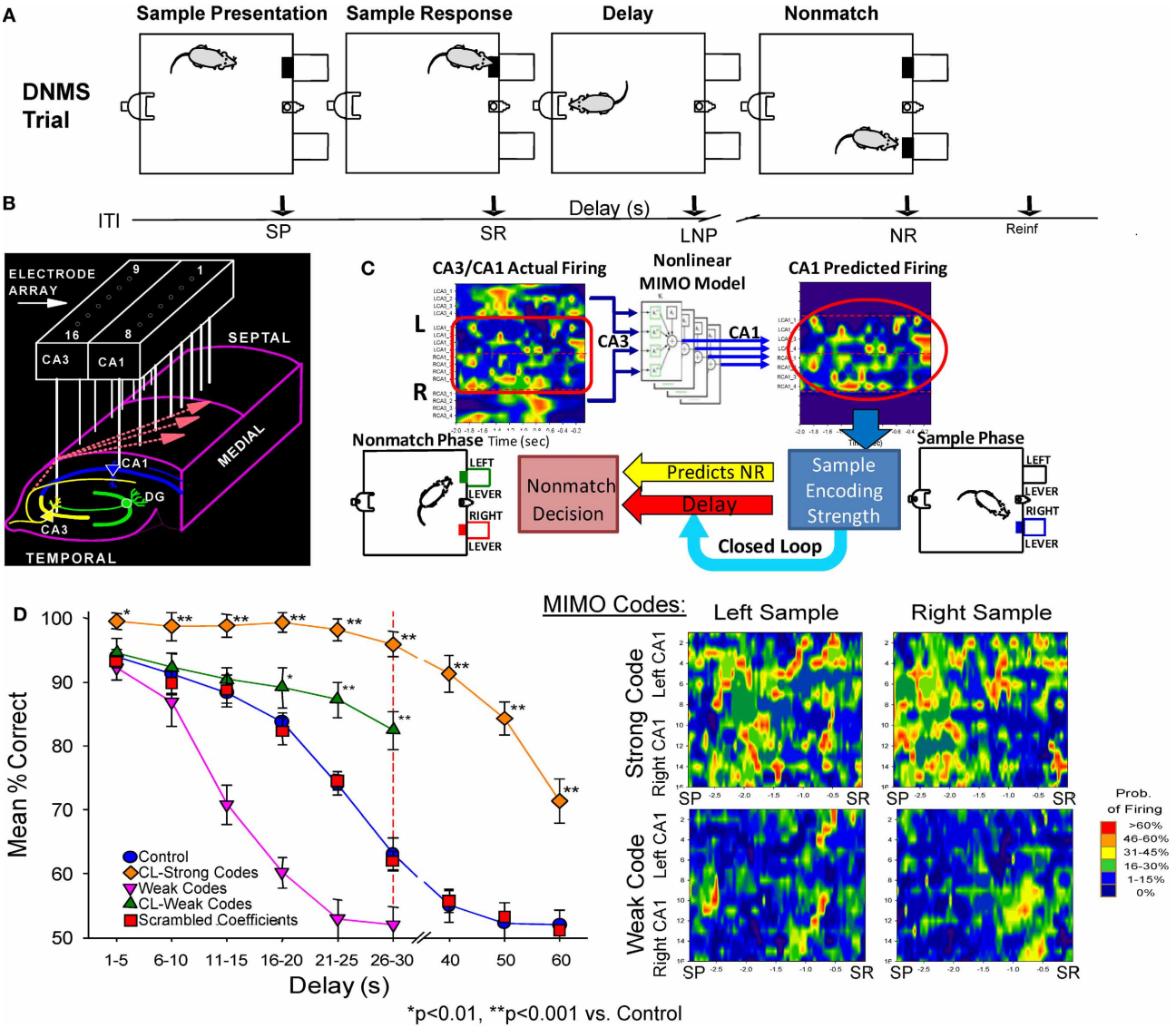

FIGURE 1 | Delayed non-match to sample (DNMS) task, MIMO model and associated hippocampal ensemble activity. (A) *DNMS Trial Diagram.* Sample lever presentation (SP) and Sample response (SR) are followed by a variable delay interval which required a nosepoke (NP) in a photocell on opposite wall. The Non-match phase began after delay timeout, with both levers presented simultaneously for reward contingent Non-match Response (NR) on the lever opposite the SR position. Correct non-match responses produced 0.2 ml of water delivered to the trough between the levers. Timeline below shows sequence of task phases: ITI–intertrial interval; SP–Sample Lever presentation; SR–Sample response; Delay–Delay interval; LNP–last required nosepoke during Delay; NR–Non-match (decision) response; Reinf.—Delivery of water reward. **(B)** Hippocampal recording array: two rows of 8 stainless steel 20 μm wires positioned longitudinally within hippocampus at 200 μm intervals for each electrode pair in CA3 and CA1 cell layers. Arrays were implanted bilaterally in both hippocampi providing a total of 32 indwelling chronic electrodes per animal. **(C)** Heatmap display (left) showing online array monitored hippocampal ensemble single neuron (actual firing) activity. Low-to-high (blue-to-red) firing rates are indicated at the separate CA3/CA1 locations on the array **(B)** during the occurrence of the SR (time 0.0 s). Schematic of non-linear MIMO model: Spike trains X_1–X_8 recorded from CA3 electrodes (CA3 input) on the hippocampal array (left) are input to the model and used to predict CA1 firing across the other 8 recording locations shown in the diagram on the right (1–8, predicted CA1) at the time of the SR. The schematic of the non-linear analysis used to construct the CA1 predicted outputs which illustrates estimation of the spatiotemporal relationship between each CA1 output (Y) and multiple CA3 inputs (X) modeled via Volterra kernels which are then combined to form the MIMO model for all CA1 locations (see Supplemental Material). The output of the model (right) is then employed to vary the delay interval of the DNMS task on the same trial in a closed loop manner as shown by the diagram below. Lower Right: MIMO Codes: Heatmap displays of MIMO model predicted CA1 firing in both hemispheres during the response on the Sample lever on individual trials during sample presentation (SP and response (SR) for trials both Left and Right sample lever presentation. Strong Codes: MIMO predicted CA1 sample lever firing on *successful trials*. Weak Codes: MIMO prediction of the same CA1 cell firing on *error trials*. Firing rates indicated by the scale bar at right. **(D)** MIMO mediated closed loop control of DNMS performance (mean ± s.e.m. % correct) summed over all animals, $n = 15$). Trials in which *strong (diamonds) and weak (triangles) SR codes* occurred are plotted as a function of length of delay, shown compared to Control performance on trials not sorted by code strength. Performance on trials with extended delays (40, 50, or 60 s, vertical dashed line) was significantly higher than on trials with the same delays (Control, 40–60 s) presented without

(Continued)

FIGURE 1 | Continued
MIMO Closed Loop regulation [$F_{(1,\ 401)} = 18.39$, $p < 0.001$, $^{*}p < 0.01$, $^{**}p < 0.001$, Closed Loop vs. Control trials]. DNMS (performance) for trials of 1–30 s delay (Control) is also shown compared to performance on trials in which only *weak SR codes* (Weak Codes) occurred [$F_{(1,\ 401)} = 11.81$, $p < 0.001$]. Performance on trials in which the MIMO model coefficients were randomly assigned (i.e., scrambled) to CA1 firing are also shown in the curve for scrambled coefficients (squares) as having no difference from Control performance.

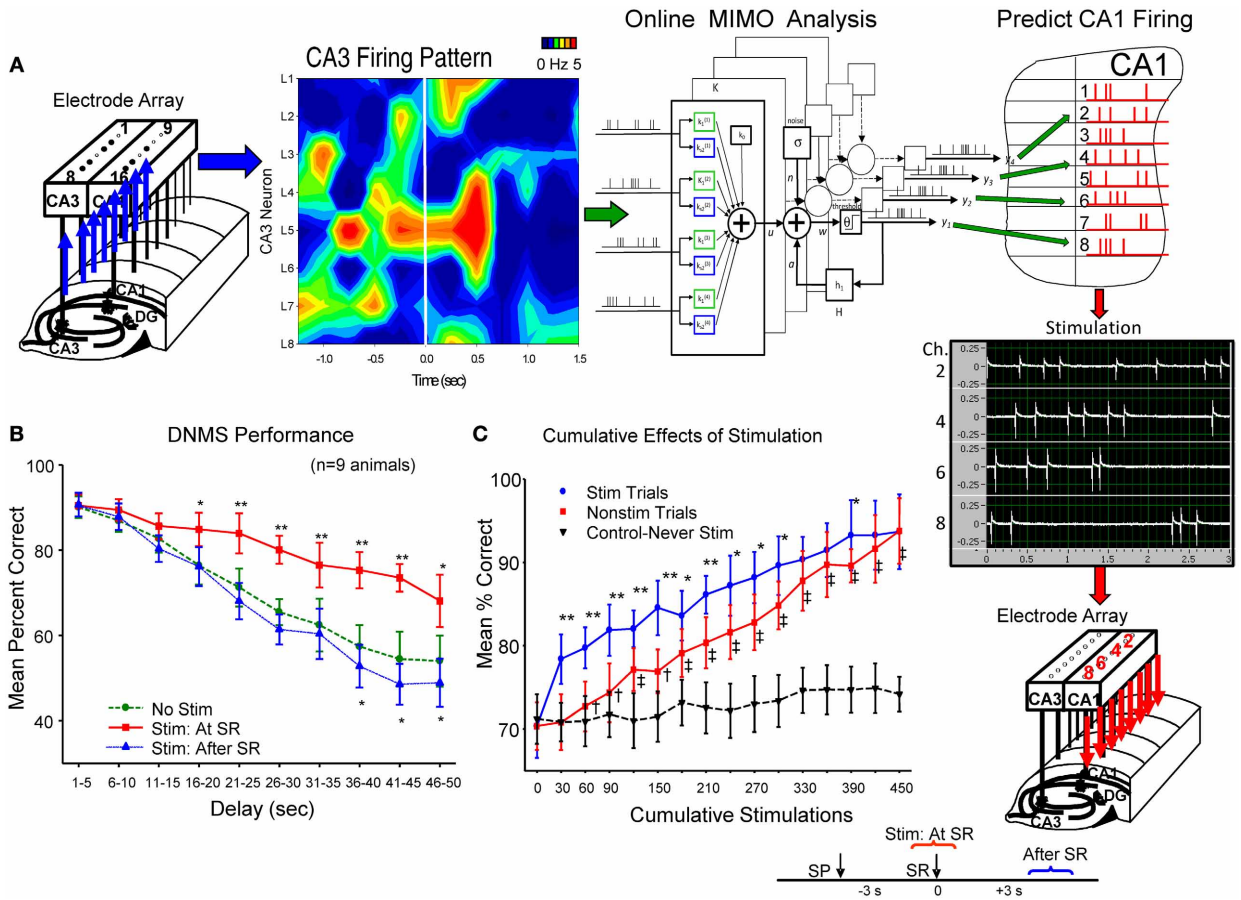

FIGURE 2 | Electrical stimulation utilizing MIMO predicted CA1 output patterns, facilitates DNMS performance. (A) Patterns of recorded CA3 cell firing in hippocampal array, shown as a heatmap (left), constitutes the input for online implementation of the MIMO model (center) to predict CA1 firing pattern (**Figure 1C**) indicated by red "tick" marks in hippocampal (CA1) layout (at right). This MIMO output pattern is fed to a programmable 8 channel stimulator (Supplemental Material) which delivers up to 3.0 s trains of bipolar electrical stimulation pulses (middle right) to the CA1 electrode locations showing the same firing pattern in each hemisphere. Stimulator output (photo display) is shown for 4 of the 8 channels to indicate different frequencies and intensities of stimulus trains delivered to separate CA1 locations (Supplemental Material). The time lag between CA3 recording, MIMO calculation and output of CA1 stimulation was approximately 50 ms. **(B)** DNMS performance graph of trained animals ($n = 9$) for delays of 1–60 s compares effects of 3.0 s stimulation delivered either: (1) at the time the SR occurred (Stim at SR) vs. No Stim [$F_{(1,\ 731)} = 11.50$, $p < 0.001$], or (2) delayed for 3.0 s after the SR was made (Stim after SR) vs. No Stim [$F_{(1,\ 731)} = 3.17$, n.s.] (see inset lower right). Asterisks ($^{*}p < 0.01$, $^{**}p < 0.001$) indicate significant difference in DNMS performance compared to control (No Stim.) trials (Berger et al., 2011). **(C)** Cumulative effects of MIMO generated SR stimulation over successive trials (Hampson et al., 2012a) shows progressive increase in overall mean (± s.e.m.) % correct performance in 30 trial blocks for animals ($n = 5$) receiving 25–30 SR stimulation trials (Stim Trials) per session for 15 sessions. Red curve (squares) shows overall performance on remaining trials within the same behavioral sessions in which no stimulation was delivered (No Stim). Inverted triangles (dotted line) shows performance over the same number of successive trials of equivalently trained animals ($n = 20$) that never received SR stimulation (Never Stim). Stim vs. Non-stim trials: $F_{(1,\ 145)} = 9.42$, $^{*}p < 0.01$,$^{**}p < 0.001$, Stim. vs. Never Stim: $F_{(1,\ 1349)} = 15.72$, $p < 0.001$, Non-stim vs. Never Stim. $F_{(1,\ 1349)} = 11.29$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$.

on stimulation trials in comparison to trials in which no stimulation was delivered (No Stim). To control for other possible actions, the specificity of the CA1 stimulation pattern with respect to encoding of the SR was tested directly by delaying delivery of the same stimulation pattern to CA1 until 3.0 s after the SR which as shown in **Figure 2B** (Stim after SR) produced no changes in performance from control (No Stim) levels. Further verification was revealed by comparing trials in which SR CA1 stimulation was generated from different MIMO firing patterns with "scrambled" coefficients between neurons (**Figure 1D**) which actually

impaired performance in some cases as shown in other studies (Hampson et al., 2012a). A final test of the similarity of the stimulation patterns to actual CA1 output firing patterns was assessed by repeating the procedure over several sessions and examining the trial-by-trial cumulative effects of continued exposure to MIMO predicted SR CA1 stimulation as shown in **Figure 2C** (Berger et al., 2011; Hampson et al., 2012b). These procedures verify that functional encoding of the SR could be imposed in subjects performing the DNMS task by matching the MIMO predicted CA1 firing pattern with stimulation pulses delivered within 50 ms to the same CA1 loci (**Figure 2A**), which provided encoding of lever position necessary to perform the task successfully across all interposed delay intervals.

A METHOD FOR TRANSFER OF MIMO SR STIMULATION FROM *DONOR* TO DELAY-NAïVE *RECIPIENT* ANIMALS

The above MIMO model SR CA1 stimulation method served as the basis for testing a unique dual animal "*donor/recipient*" paradigm in which (1) a well-trained "*donor rat*" performed the DNMS task in one chamber at the same time as (2) a delay-naïve "*recipient rat*" was tested at the same time in a different chamber in a trial synchronized manner (**Figure 3A**). The "*recipient rat*" was not trained to perform the DNMS task over intervening delay intervals >1.0–3.0 s (red dotted delay phase in **Figure 3B**) which was the time it took to make the required nosepoke response on the opposite wall of the chamber to present the Non-match phase (**Figure 1A**). The imposition of trials with extended delay intervals during the session constituted the first exposure of *recipient rats* to the task requirement for retention of SR information across increased time intervals (8–16 s) in order to correctly select the opposite lever in the Non-match phase (Hampson et al., 2008). Performance in the Sample phase of the task was synchronized between animals by presentation of the Sample lever in the same position at the same time in both chambers to initiate the same trial simultaneously for both animals (**Figure 3B**). On synchronous trials in which the MIMO model applied to the *donor rat* CA3 firing patterns, generated a successful strong code SR CA1 pattern (**Figure 2A**), the stimulus pulses representing that MIMO strong SR code were routed instead to the corresponding CA1 electrodes in the *recipient rat* (**Figure 3A**) performing the SR at approximately the same time. For the naïve *recipient rat* following the delivery of the *donor rat* strong code SR CA1 stimulation pattern after the SR, an unfamiliar delay interval of 8, 12, or 16 s was introduced into the trial prior to onset of the Non-match phase. Since routing of SR CA1 stimulation to the *recipient rat* was determined by concurrent CA3 encoding strength in the hippocampus of the simultaneously performing *donor rat*, extended delay trials for the *recipient rat* occurred randomly within the paired sessions. As a control procedure, performance was compared on trials with the same delays administered to *recipient rats* by *donor rat* CA3 encoding strength on the same trial but without delivery of SR CA1 stimulation.

RESULTS

TRANSFER OF MEMORY TO DELAY-NAïVE *RECIPIENT* ANIMALS BY DELIVERY OF MIMO STIMULATION FROM TRAINED *DONOR* ANIMALS

The employment of *donor rat* MIMO model generated SR CA1 stimulation was applied to test whether it was possible to facilitate performance in *delay-naïve recipient rats* untrained in the delay version of the DNMS task. Results in **Figure 4A** show the mean % correct performance of 5 different *recipient rats* subjected for the first time to 8, 12, and 16 s interpolated delays with MIMO derived SR CA1 stimulation patterns (Stim) delivered on half the trials from synchronously performing *donor rats. Donor rat* SR CA1 stimulation allowed *recipient rats* to perform significantly better than if they did not receive stimulation (No stim) and these levels are compared with their higher performance on trials in which no delay was interspersed (0.0 s). The overall performance of all *recipient* is shown in **Figure 4B** for recipient-stim and recipient-no stim trials in which highly significant improved performance is apparent across all delays. **Figure 4B** also shows that recipient-stim average performance was significantly below that of fully trained animals that did not receive SR stimulation at those same delays (trained subjects, $n = 23$).

The physiologically specific nature of the *donor rat* stimulation was further verified by the fact that performance was facilitated in a delay dependent manner (**Figures 4A,B**) in the same way that natural performance was affected by the duration of interposed delays during the trial. This was further verified by comparing the effects of MIMO stimulation patterns delivered by different *donor rats* to the same *recipient rat* within, as well as, across different behavioral sessions. **Figure 5A** shows the comparison of performance of the same *recipient rat* receiving SR stimulation from two different *donor rats* over similar interposed delay trials. **Figure 5A** shows the patterns of SR CA1 stimulation delivered by each *donor rat (donor rats 1 and 2)* on both left and right SR lever trials. Although there were slight differences with respect to the spatiotemporal delivery of CA1 stimulation pulses, the overall patterns related to the time of execution of the SR were highly similar. The graphs to the right in **Figure 5A** show the average performance of the same *recipient rat* on similar types of trials with stimulation and non-stimulated extended delays from the same two *donor rats.* It is clear that stimulation generated by both *donor* rats on different trials in the same session facilitated performance of the *recipient rat* in nearly identical fashion. **Figure 5B** summarizes the performance of all *recipient rats* ($n = 5$) over the 3 delay intervals for all *donor rat* ($n = 6$) stimulation (Stim) vs. non-stimulated (Non-Stim) trials compared to trials in which no delay was imposed (0 s).

Control manipulations performed to insure that *donor rat* SR stimulation was the basis for the improved performance of *recipient rats* included: (1) changing the *donor rat* stimulation patterns in different ways such as scrambling coefficients (**Figure 1A**), (2) delivering *donor rat* stimulation patterns at different times (i.e., 3.0 s) after the SR (**Figure 2B**), and (3) delivery of stimulation based on *recipient rat* MIMO-extracted SR CA1 patterns on the trials with interpolated delays determined by *donor rat* encoding patterns (not shown). None of the latter control procedures produced significant increases in *recipient rat* performance above that exhibited on trials with the same delays and no *donor rat* stimulation (**Figure 4** No Stim, **Figure 5B**).

NEURAL BASIS FOR MIMO STIMULATION ENHANCED MEMORY

A major factor that relates to the above demonstration of enhanced memory in the *donor* as well as *delay-naïve recipient rats*, is the actual neural basis for the enhancement invoked

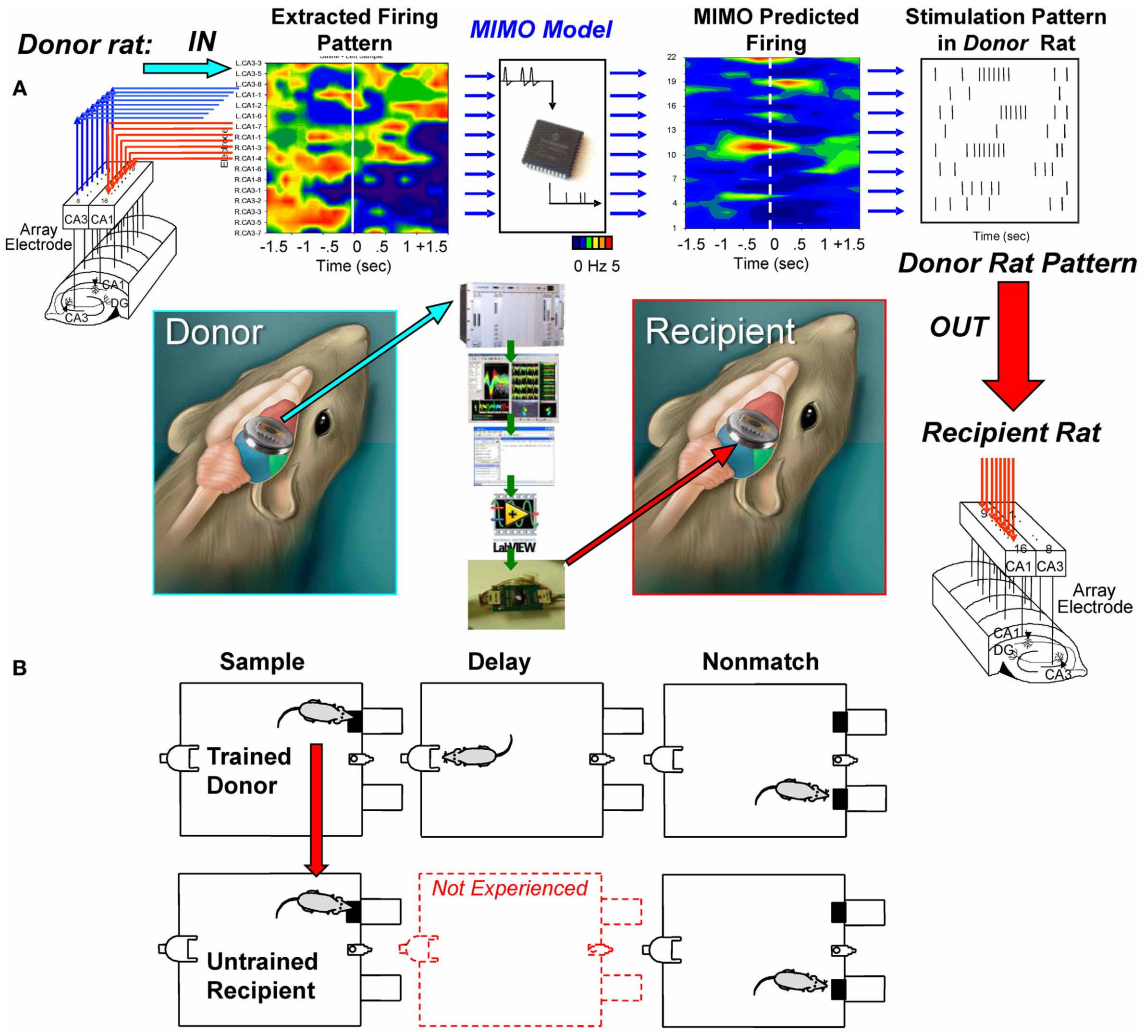

FIGURE 3 | Transference of successful MIMO coded ensemble firing patterns from trained "*donor*" rats to task-naïve "*recipient*" rats. **(A)** Recordings were obtained online from well-trained animals (i.e., *donor rats*) with validated effective MIMO SR CA1 stimulation patterns as shown in **Figure 2**. A second group of delay-naïve animals (*recipient rats*) were only trained to perform the operant responses in the DNMS task in sequence without exposure to variable and extended delay intervals interposed between the SR and NR task phases requiring completion of the nosepoke response on the opposite wall (red middle diagram). **(B)** *Donor-Recipient rat* "pairs" were recorded from and tested simultaneously in different chambers with DNMS trial execution synchronized by presentation of the sample lever in the same position at the same time. During performance of trials within the simultaneous sessions, *donor rat* hippocampal ensemble activity was monitored for presence of CA3 firing predictions of effective *strong SR code* CA1 stimulation patterns (**Figure 2**). When such *donor rat* strong code patterns occurred, the associated MIMO-predicted SR CA1 stimulation pattern was routed instead to the CA1 electrodes in the *recipient rat* hippocampus while performing the *SR* within 1–3 s after detection of *donor rat* strong SR code. Delay intervals of 8, 12, or 16s were then introduced on the same trial for the *recipient rat* which required the previously learned selection of the opposite lever in the Non-match phase of the task after timeout of the unfamiliar delay periods. All trials on which delays were imposed to *recipient rats* were determined when strong SR codes were generated by *donor rats*; hence occurrence of all delay trials during *recipient rat* sessions was essentially random and unpredictable.

by delivery of MIMO SR CA1 stimulation and also the type of changes that occur under normal conditions related to improved vs. impaired performance in the same subjects. The influence of administered MIMO CA1 stimulation on synaptic connectivity during the session was assessed using local field potentials (LFPs) recorded from each of the 8 CA1 locations generated by stimulating a single electrode location in CA3 on the same array (**Figure 6A**) with min-to-max voltage ranges. For these LFPs, it was possible to assess changes in identified voltage LFP components related to excitatory and inhibitory synaptic inputs (Hampson et al., 1989; Truccolo et al., 2002; Leung, 2011). CA1 LFPs were assessed before and after sessions in which MIMO stimulation was delivered and facilitated performance vs. sessions in which no stimulation was delivered. The most effective method of assessing such changes was to characterize differences in LFP waveforms by subtracting pre-session LFPs from post-session LFPs and comparing voltages (Post-Pre_{diff}) in 10 ms segments as shown in **Figure 6B**. The resulting Post-Pre_{diff} waveforms reflect changes in particular components of the LFP generated from the same CA3 stimulation location related to both excitatory and

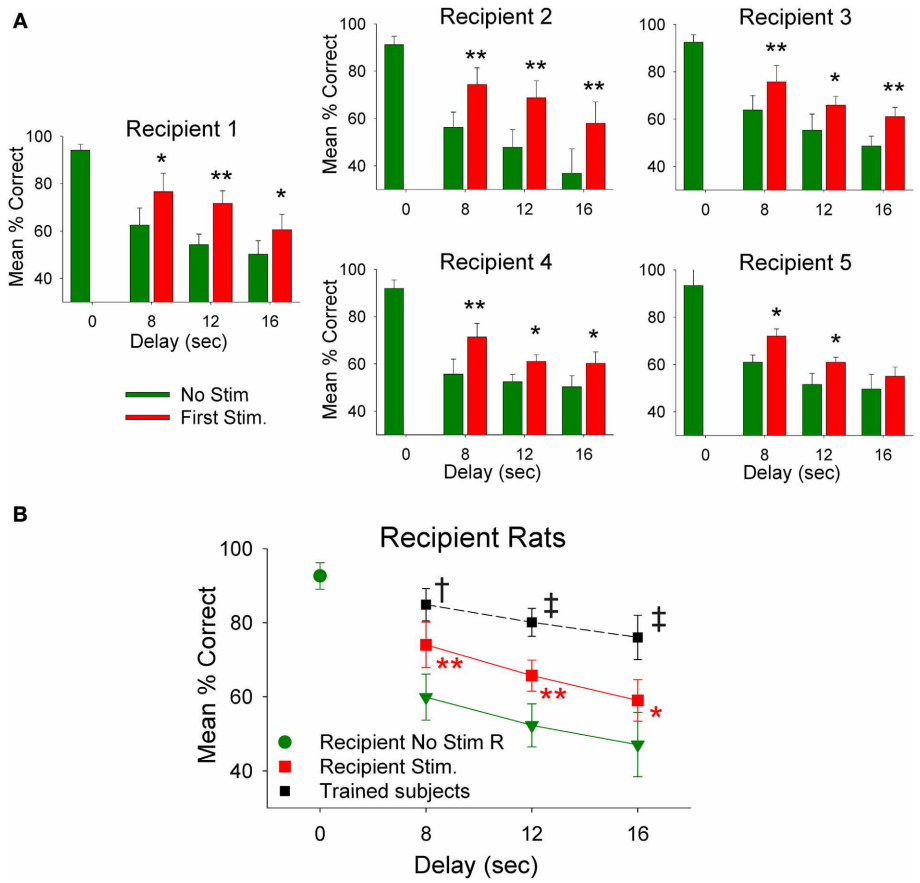

FIGURE 4 | *Recipient rat* performance on DNMS trials with unfamiliar superimposed delays facilitated by *donor rat* mediated SR stimulation. (A) Individual DNMS performance of five different *recipient rats* subjected to trials with 8, 12, and 16 s delays shown for trials in which no stimulation was delivered (No Stim) or on trials on which a simultaneously paired *donor rat* delivery of MIMO SR CA1 stimulation pattern was delivered (Stim). The similarity across each graph indicates generality of facilitated performance on imposed delay trials with delivery of *donor rat* MIMO generated CA1 SR stimulation. Asterisks $^{*}p < 0.01$, $^{**}p < 0.001$, Stim *donor rat* vs. No Stim. **(B)** Overall performance of *recipient rats* ($n = 5$) is shown as mean (±s.e.m.) % correct trials with no delays (green dot−0.0 s values) in comparison to trials with variable delays (8, 12, 16 s) without *donor rat* stimulation (green triangles-No Stim) delivered during the trial [$F_{(3,\ 279)} = 3.61$, $p < 0.001$]; and performance on trials with the same delays but including *donor rat* MIMO strong SR code stimulation (Recipient Stim, red squares) which significantly improved performance compared to No Stim trials [$F_{(1,\ 279)} = 9.82$, $p < 0.001$]. For comparison a plot of the average performance level of rats fully trained ($n = 20$) on the task at the same delays (Trained subjects) is shown (black squares) for comparison to *recipient rat* performance on stimulated trials [$F_{(1,\ 1349)} = 13.48$, $p = 0.001$, Trained subjects > *recipient rats*]. Symbols: $^{*}p < 0.01$, $^{**}p < 0.001$, $^{\dagger}p < 0.01$, $^{\ddagger}p = 0.001$.

inhibitory input over the same range of voltages, before and after behavioral sessions in which SR stimulation was, or was not, delivered.

Figure 6B shows the average of Post-Pre$_{diff}$ LFP waveforms for a single trained animal following SR stimulation (blue) vs. non-stimulation (red) sessions. It is clear that the LFP changes were related directly to both excitatory (40–80 ms) and inhibitory (90–175 ms) components of well-characterized LFPs recorded from the cell layer at each of the eight CA1 locations (Leung, 2011). The lack of as much change in Post-Pre$_{diff}$ LFP measures for non-stimulation (red curve) vs. SR stimulation (blue curve) sessions in **Figure 6B** reflects the increase in excitatory synaptic input to the same CA1 locations that received strong code SR CA1 stimulation patterns and facilitated performance during the behavioral sessions in the same animal. To demonstrate a more general feature of this effect, the dotted curve in **Figure 6B** reflects a further difference of the LFP Post-Pre$_{diff}$ values in terms of subtracted Stim session Post-Pre$_{diff}$ LFP waveforms from similar Non-stim session waveforms, i.e., Diff$_{stim}$—Diff$_{non-stim}$ LFP values. Thus, the dotted curve in **Figure 6B** reflects the average differences in LFPs across 5 individual animals calculated in the same manner as the two Post-Pre$_{diff}$ LFP difference curves (red and blue) but using Post-Pre$_{diff}$ LFPs instead to provide the resulting dotted curve average difference of LFP waveform for SR stim vs. non-stim sessions (i.e., Diff$_{stim}$—Diff$_{non-stim}$). Since this average difference (Diff$_{stim}$—Diff$_{non-stim}$) across all animals ($n = 5$) reflects alteration in the same LFP components as shown for individual waveforms in a single animal (red and blue Post-Pre$_{diff}$ LFPs), it is clear that synaptic processes mediating CA3-to-CA1 transmission were increased by MIMO stimulation delivery during the DNMS sessions in which performance within and between animals was facilitated (**Figures 4**, **5**).

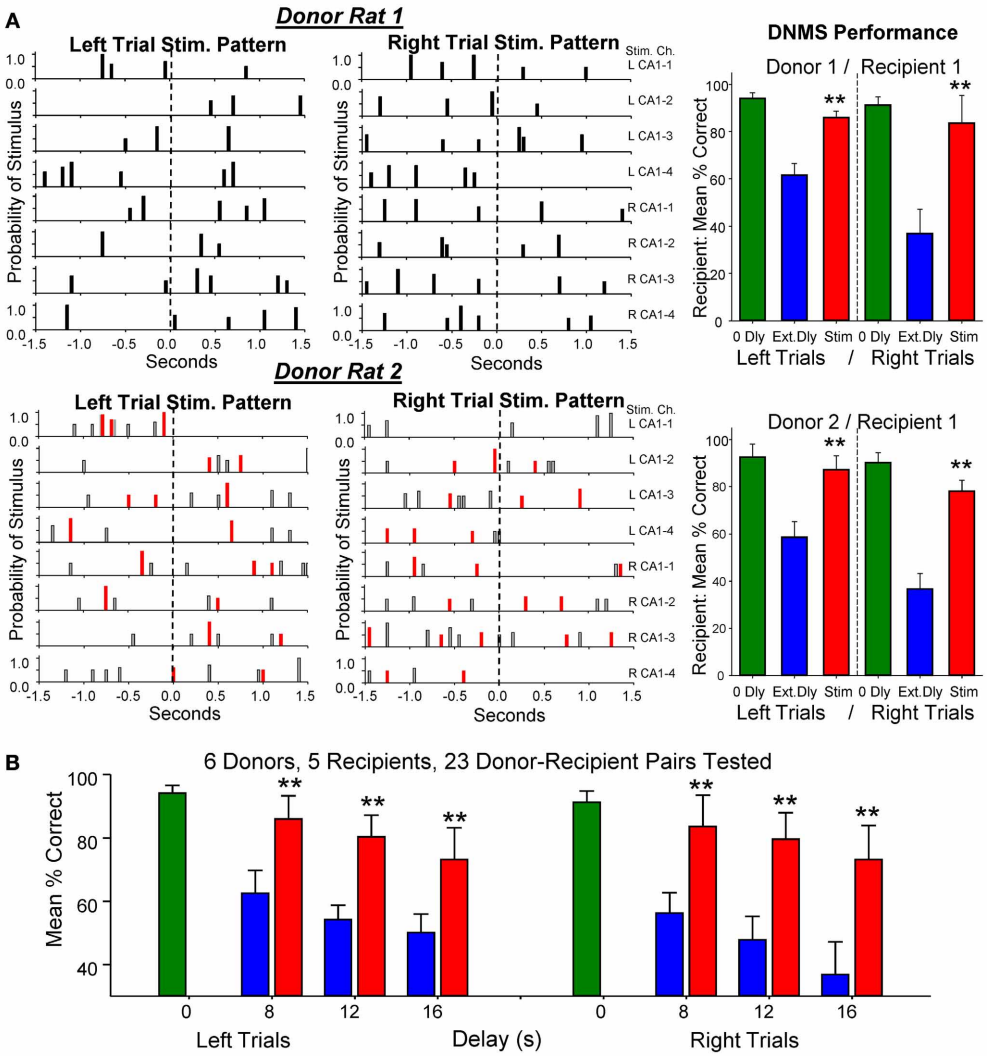

FIGURE 5 | Enhancement of performance of the same *recipient rat* by different *donor rats.* (A) Left: Delivered MIMO SR CA1 stimulation patterns showed for left and right lever trials from *Donor rat 1* (upper) and *Donor rat 2* (lower). Red marks in *Donor rat 2* patterns reflect occurrences of identical pulses delivered in *Donor rat 1* pattern (above) for direct comparison of the two SR Stimulation patterns delivered to the same *Recipient rat* on different trials. Right: Overall performance of the same *Recipient rat* for sessions in which SR Stimulation (Stim) on delay trials was contributed by *Donor rat 1* (upper) and *Donor rat 2* (lower) for left and right Sample lever trials summed over all delays (red) compared with delay trials in which SR stimulation was not delivered (blue). Green bars represent performance by the same *Recipient rat* on trials with no delay (0 Dly) presented in the same sessions as described above. **(B)** Lower plot shows overall average performance for all *Donor/Recipient* sessions ($n = 23$) for trials with Left and Right SR position and those which received *donor rat* SR stimulation (red) vs. no stimulation trials (blue) as a function of delay (0, 8, 12, 16 s). Plots include all *Donor/Recipient* pairs, 5 different *recipient rats* paired with one or more *donor rats* ($n = 6$). Asterisks (**$p < 0.001$) indicate significant difference compared to trials with no *donor rat* stimulation (No Stim).

DISCUSSION

DONOR/RECIPIENT RECOVERY OF HIPPOCAMPAL MEMORY: A MODEL FOR APPLICATION TO MEMORY DEFICITS

The above findings provide highly significant evidence that functional working memory can be enhanced by delivery of *donor rat* MIMO CA1 patterned electrical stimulation to the CA1 field in the hippocampus of *recipient rats.* This shows that information encoded by individual neural events in naïve *recipient rats* can be effectively altered by substitution of *donor rat* MIMO derived electrical stimulus patterns in the same manner as demonstrated in prior studies in which effective stimulus trains were generated by, and delivered to, the same animal (Berger et al., 2011; Hampson et al., 2012a). The demonstration of improved task performance in naïve *recipient rats* (**Figures 4**, **5**), verifies that *donor rat* SR CA1 stimulation was capable of inducing the type of encoding process necessary when facilitated retention of information was required because of interposed unfamiliar delays of variable duration (**Figure 6**). The fact that MIMO stimulation

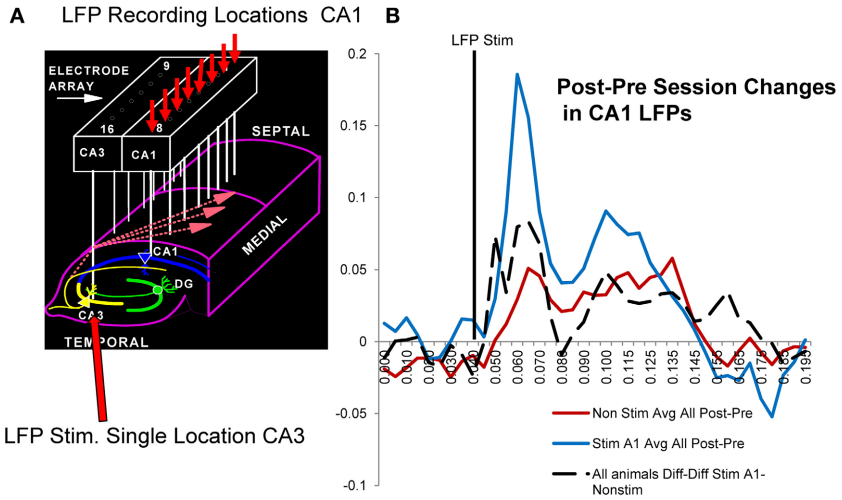

FIGURE 6 | Possible synaptic basis for facilitative *Donor/Recipient* MIMO SR stimulation. (A) Illustration of hippocampal synaptic connections between CA3 and CA1 cells in the same hippocampal region occupied by the same electrode array used to deliver SR Stimulation (**Figures 1–3**). Arrows show divergent projections from a single CA3 cell to multiple CA1 cells via Shaffer collateral connections used to determine changes in CA1 (small red arrows) local field potentials (LFPs) elicited by stimulation delivered to a single CA3 locus (large red arrow) before (Pre) and after (Post) behavioral sessions with MIMO SR Stimulation vs. non-stimulated sessions. **(B)** Average CA1 LFPs elicited by CA3 stimulation are plotted as differences (Post-Pre_{diff}) in voltage amplitude measured at the indicated time points (10 ms) of the LFP after stimulus pulse delivery (vertical black line). Red: Mean Post-Pre_{diffs} in LFP amplitudes recorded prior to and following non-stimulation sessions for trained animals. Blue: Average Post-Pre_{diffs} in LFP amplitude following sessions in which SR stimulation was delivered to facilitate performance. Positive Post-Pre_{diffs} reflect average voltage changes related to increased CA1 LFP components after the behavioral session relative to voltages elicited by the same CA3 current intensities prior to the session. These Post-Pre_{diffs} for sessions in which SR stimulation facilitated task performance (blue curve) are shown compared to Post-Pre_{diffs} for those sessions in which stimulation was not delivered (red curve). Dotted: Diff-Diff shows average difference between CA1 LFP Post-Pre_{diffs} for SR stim vs. non-stim sessions (Stim-Non-stim) measured in 6 of the *Donor rats* (all animals A1-non-stim).

can approximate normal ensemble firing involved in the encoding and retrieval of task-relevant information is consistent with other recent findings investigating relationships between multineuron firing in cortical ensembles and behavioral task requirements (Ross and Eichenbaum, 2006; Komorowski et al., 2009; Smith et al., 2009; Rouse et al., 2011). However, the demonstration that the patterns marked as effective and generated online in one animal, could be transferred via temporally matched electrical stimulation of similar CA1 regions in naïve *recipient* animals exposed to the same task contingencies, has not been shown previously. Although consistent in some ways with a recent "brain-to-brain transfer" experiment (Pais-Viera et al., 2013) in which sensorimotor cortical signals were used to influence behavioral choice in the recipient rodent, the results presented here differ significantly because in that experiment, stimulation was delivered at the time of the behavioral response, whereas in our study, the stimulation corresponded to the encoding phase of the task (SR) and was delivered up to 16 s prior to the behavioral response, confirming transfer of a *memory* code, and not simply induction of a motor response. In addition, the lack of enhancement or transfer when several control procedures were employed in the above memory transfer paradigm; i.e., temporal relation to SR, reduced stimulation intensity, closed-loop dependence, etc. (**Figures 1–5**), strongly supports the specificity of the transference of *donor rat* MIMO model derived SR information for hippocampal function to naïve *recipient rats* for task-relevant performance.

These results provide important insight for extending *donor/recipient* procedures to functions performed by other brain regions and other behavioral endpoints as shown recently (Pais-Viera et al., 2013), and eventually to similar circumstances involving humans (Boettiger and D'Esposito, 2005; Smith et al., 2009; Hasson et al., 2012). Once fabricated into a neural prosthesis for *recipients* this unique technology could (1) immediately enhance task-specific performance, (2) repair damaged or impaired task-dependent brain circuitry, and possibly even, (3) provide neural encoding of task-relevant information without prior training. The long history of investigation with hippocampal recording in the behavioral context employed, and prior collaboration perfecting application of the MIMO model to these recordings (Hampson et al., 2008, 2012a; Berger et al., 2012; Marmarelis et al., 2013; Song et al., 2013), as well as recent applications to the non-human primate hippocampus (Hampson et al., 2013) and prefrontal cortex (Hampson et al., 2012c; Opris et al., 2012), provided the insight necessary to extrapolate how *donor/recipient* memory transference could occur as demonstrated here. However, the fact that transferred patterns of electrical brain stimulation have significant functional impact and are capable of modifying performance via strategic online delivery provides another demonstration of *donor-recipient* brain compatibility (Pais-Viera et al., 2013), but this application to hippocampus for improving memory is the first demonstration specific to brain cognitive function. Such results not only provide important new insight into how hippocampal circuits can be operated to process memory-dependent information via external control, but also provide a basis for extending and/or perfecting similar *donor/recipient* type devices (Jarosiewicz et al., 2008;

Venkatraman and Carmena, 2011; Hasson et al., 2012) to enhance and/or replace memory deficiencies in humans.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnsys.2013.00120/abstract

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Systems neuroscience in focus: from the human brain to the global brain?

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INTRODUCTION

Human intelligence (i.e., the ability to consistently solve problems successfully) has evolved through the need to adapt to changing environments. This is not only true of our past but also of our present. Our brain faculties are becoming more sophisticated by cooperating and interacting with technology, specifically digital communication technology (Asaro, 2008).

When we consider the matter of brain function augmentation, we take it for granted that the issue refers to the human brain as a distinct organ. However, as we live in a complex technological society, it is now becoming clear that the issue is much more complicated. Individual brains cannot simply be considered in isolation, and their function is no longer localized or contained within the cranium, as we now know that information may be transmitted directly from one brain to another (Deadwyler et al., 2013; Pais-Vieira et al., 2013). This issue has been discussed in detail and attempts have been made to study the matter within a wider and more global context (Nicolelis and Laporta, 2011). Recent research in the field of brain to brain interfaces has provided the basis for further research and formation of new hypotheses in this respect (Grau et al., 2014; Rao et al., 2014). This concept of rudimentary "brain nets" may be expanded in a more global fashion, and within this framework, it is possible to envisage a much bigger and abstract "meta-entity" of inclusive and distributed capabilities, called the Global Brain (Mayer-Kress and Barczys, 1995; Heylighen and Bollen, 1996; Johnson et al., 1998; Helbing, 2011; Vidal, in press).

This entity reciprocally feeds information back to its components—the individual human brains. As a result, novel and hitherto unknown consequences may materialize such as, for instance, the emergence of rudimentary global "emotion" (Garcia and Tanase, 2013; Garcia et al., 2013; Kramera et al., 2014), and the appearance of decision-making faculties (Rodriguez et al., 2007). These characteristics may have direct impact upon our biology (Kyriazis, 2014a). This has been long discussed in futuristic and sociology literature (Engelbart, 1988), but now it also becomes more relevant to systems neuroscience partly because of the very promising research in brain-to-brain interfaces. The concept is grounded on scientific principles (Last, 2014a) and mathematical modeling (Heylighen et al., 2012).

AUGMENTING BRAIN FUNCTION ON A GLOBAL SCALE

It can be argued that the continual enhancement of brain function in humans, i.e., the tendency to an increasing intellectual sophistication, broadly aligns well with the main direction of evolution (Steward, 2014). This tendency to an increasing intellectual sophistication also obeys Ashby's Law of Requisite Variety (Ashby, 1958) which essentially states that, for any system to be stable, the number of states of its control mechanisms must be greater than the number of states in the system being controlled. This means that, within an ever-increasing technological environment, we must continue to increase our brain function (mostly through using, or merging with, technology such as in the example of brain to brain communication mentioned above), in order to improve integration and maintain stability of the wider system. Several other authors (Maynard Smith and Szathmáry, 1997; Woolley et al., 2010; Last, 2014a) have expanded on this point, which seems to underpin our continual search for brain enrichment.

The tendency to enrich our brain is an innate characteristic of humans. We have been trying to augment our mental abilities, either intentionally or unintentionally, for millennia through the use of botanicals and custom-made medicaments, herbs and remedies, and, more recently, synthetic nootropics and improved ways to assimilate information. Many of these methods are not only useful in healthy people but are invaluable in age-related neurodegenerative disorders such as dementia and Parkinson's disease (Kumar and Khanum, 2012). Other neuroscience-based methods such as transcranial laser treatments and physical implants (such as neural dust nanoparticles) are useful in enhancing cognition and modulate other brain functions (Gonzalez-Lima and Barrett, 2014).

However, these approaches are limited to the biological human brain as a distinct agent. As shown by the increased research interest in brain to brain communication (Trimper et al., 2014), I argue that the issue of brain augmentation is now embracing a more global aspect. The reason is the continual developments in technology which are changing our society and culture

(Long, 2010). Certain brain faculties that were originally evolved for solving practical physical problems have been co-opted and exapted for solving more abstract metaphors, making humans adopt a better position within a technological niche.

The line between human brain function and digital information technologies is progressively becoming indistinct and less well-defined. This blurring is possible through the development of new technologies which enable more efficient brain-computer interfaces (Pfurtscheller and Neuper, 2002), and recently, brain-to-brain interfaces (Grau et al., 2014).

We are now in a position expand on this emergent worldview and examine what trends of systems neuroscience are likely in the near-term future. Technology has been the main drive which brought us to the position we are in today (Henry, 2014). This position is the merging of the physical human brain abilities with virtual domains and automated web services (Kurzweil, 2009). Modern humans cannot purely be defined by their biological brain function. Instead, we are now becoming an amalgam of biological and virtual/digital characteristics, a discrete unit, or autonomous agent, forming part of a wider and more global entity (**Figure 1**).

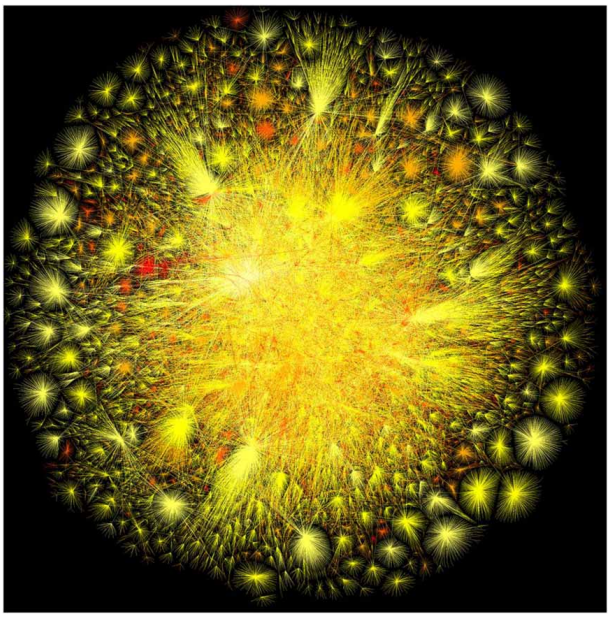

FIGURE 1 | Computer-generated image of internet connections world-wide (Global Brain). The conceptual similarities with the human brain are remarkable. Both networks exhibit a scale-free, fractal distribution, with some weakly-connected units, and some strongly-connected ones which are arranged in hubs of increasing functional complexity. This helps protect the constituents of the network against stresses. Both networks are "small worlds" which means that information can reach any given unit within the network by passing through only a small number of other units. This assists in the global propagation of information within the network, and gives each and every unit the functional **potential** to be directly connected to all others. *Source: The Opte Project/Barrett Lyon. Used under the Creative Commons Attribution-Non-Commercial 4.0 International License.*

LARGE SCALE NETWORKS AND THE GLOBAL BRAIN

The Global Brain (Heylighen, 2007; Iandoli et al., 2009; Bernstein et al., 2012) is a self-organizing system which encompasses all those humans who are connected with communication technologies, as well as the emergent properties of these connections. Its intelligence and information-processing characteristics are distributed, in contrast to that of individuals whose intelligence is localized. Its characteristics emerge from the dynamic networks and global interactions between its individual agents. These individual agents are not merely the biological humans but are something more complex. In order to describe this relationship further, I have introduced the notion of the noeme, an emergent agent, which helps formalize the relationships involved (Kyriazis, 2014a). The noeme is a combination of a distinct physical brain function and that of an "outsourced" virtual one. It is the intellectual "networked presence" of an individual within the GB, a meaningful synergy between each individual human, their social interactions and artificial agents, globally connected to other noemes through digital communications technology (and, perhaps soon, through direct brain to brain interfaces). A comparison can be made with neurons which, as individual discrete agents, form part of the human brain. In this comparison, the noemes act as the individual, information-sharing discrete agents which form the GB (Gershenson, 2011). The modeling of noemes helps us define ourselves in a way that strengthens our rational presence in the digital world. By trying to enhance our information-sharing capabilities we become better integrated within the GB and so become a valuable component of it, encouraging mechanisms active in all complex adaptive systems to operate in a way that prolongs our retention within this system (Gershenson and Fernández, 2012), i.e., prolongs our biological lifespan (Kyriazis, 2014b; Last, 2014b).

DISCUSSION

This concept is a helpful way of interpreting the developing cognitive relationship between humans and artificial agents as we evolve and adapt to our changing technological environment. The concept of the noeme provides insights with regards to future problems and opportunities. For instance, the study of the function of the noeme may provide answers useful to biomedicine, by coopting laws applicable to any artificial intelligence medium and using these to enhance human health (Kyriazis, 2014a). Just as certain physical or pharmacological therapies for brain augmentation are useful in neurodegeneration in individuals, so global ways of brain enhancement are useful in a global sense, improving the function and adaptive capabilities of humanity as a whole. One way to augment global brain function is to increase the information content of our environment by constructing smart cities (Caragliu et al., 2009), expanding the notion of the Web of Things (Kamilaris

et al., 2011), and by developing new concepts in educational domains (Veletsianos, 2010). This improves the information exchange between us and our surroundings and helps augment brain function, not just physically in individuals, but also virtually in society.

Practical ways for enhancing our noeme (i.e., our digital presence) include:

- Cultivate a robust social media base, in different forums.
- Aim for respect, esteem and value within your virtual environment.
- Increase the number of your connections both in virtual and in real terms.
- Stay consistently visible online.
- Share meaningful information that requires action.
- Avoid the use of meaningless, trivial or outdated platforms.
- Increase the unity of your connections by using only one (user)name for all online and physical platforms.

These methods can help increase information sharing and facilitate our integration within the GB (Kyriazis, 2014a). In a practical sense, these actions are easy to perform and can encompass a wide section of modern communities. Although the benefits of these actions are not well studied, nevertheless some initial findings appear promising (Griffiths, 2002; Granic et al., 2014).

CONCLUDING REMARKS

With regards to improving brain function, we are gradually moving away from the realms of science fiction and into the realms of reality (Kurzweil, 2005). It is now possible to suggest ways to enhance our brain function, based on novel concepts dependent not only on neuroscience but also on digital and other technology. The result of such augmentation does not only benefit the individual brain but can also improve all humanity in a more abstract sense. It improves human evolution and adaptation to new technological environments, and this, in turn, may have positive impact upon our health and thus longevity (Solman, 2012; Kyriazis, 2014c).

In a more philosophical sense, our progressive and distributed brain function amplification has begun to lead us toward attaining "god-like" characteristics (Heylighen, in press) particularly "omniscience" (through Google, Wikipedia, the semantic web, Massively Online Open Courses MOOCs—which dramatically enhance our knowledge base), and "omnipresence" (cloud and fog computing, Twitter, YouTube, Internet of Things, Internet of Everything). These are the result of the outsourcing of our brain capabilities to the cloud in a distributed and universal manner, which is an ideal global neural augmentation. The first steps have already been taken through brain to brain communication research. The concept of systems neuroscience is thus expanded to encompass not only the human nervous network but also a global network with societal and cultural elements.

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The overlooked potential for social factors to improve effectiveness of brain-computer interfaces

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Introduction

The surge in development of brain-computer interface (BCI) devices is highly focused on the algorithms, mechanics, and neurophysics of their production (Lebedev and Nicolelis, 2006; Lebedev et al., 2011; Opris, 2013). Here I propose that capitalizing on research findings from the field of social neuroscience can enhance training and effectiveness of BCI devices. BCIs are not just about individual brains but also about brains in interaction with other brains. Learning in a social context is more effective than non-social instruction and countless neurophysiology studies have demonstrated that social interaction actually alters physiology, including changes in neuroplasticity and arousal. Importantly, social interaction also consists of emotional responses that have powerful rewarding qualities and incur reciprocal action. Interdisciplinary cooperation between social neuroscience and BCI innovation has been proposed to promote development of more effective BCIs that demonstrate adaptability during interaction (Mattout, 2012). The challenges of BCI illiteracy, or BCI inefficiency, suggests a vital need to consider all possible contributing factors to decrease the failure rate seen in up to a third of users (Vidaurre and Blankertz, 2010). Additionally, it has been suggested that BCI inefficiency can be reduced by addressing flaws in human training approaches, which have been largely neglected (Lotte et al., 2013). Therefore, the social cues and contexts a patient has when BCIs are integrated and employed should not be overlooked for their potential to improve effectiveness.

Social Intelligence

The human brain, like other primate brains, has evolved to be exquisitely tuned to social interactions (Ghazanfar and Santos, 2004). In fact, sociality might have been the primary force driving the evolution of primate intelligence (Jolly, 1966; Humphrey, 1976; Dunbar and Shultz, 2007). Thus, it is no leap to assume that cognitive abilities would be influenced by social interactions (Ybarra et al., 2008). Importantly, cognitive abilities do not exist as abstract mental activities independent of body and world (Barrett and Henzi, 2005). We are born into an environment that consists of others acting and interacting; successfully navigating this social milieu requires the development of many cognitive skills. These essential capacities include memory, learning, decision-making, and behavioral inhibition as well as more complex abilities such as communicating, problem-solving, teaching, mentalizing, and inferring others' mental states (Gariépy et al., 2014).

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Social Cues and Contexts

Social contexts include observing and participating in exchanges between individuals, and responding to cues integral to social behavior. These cues include complex stimuli that require simultaneous processing of multiple sensory inputs, including olfactory, auditory, tactile, and visual cues. The emotional responses of self and others are also social cues. Whom we are interacting with matters, as well as the connection we feel with them along a continuum ranging from perceived social isolation to bonding and attachment (Cacioppo and Cacioppo, 2012). The mere presentation of cues specific to social interaction, such as language or images of the same species, is enough to cause neurophysiological changes in brain and behavior. In primates, many studies take advantage of the fact that pictures of objects, abstract images, or other species are not as rewarding as pictures of conspecifics (Wilson and Goldman-Rakic, 1994). Even the nature of the stimulus is relevant—we have a preference for biological movement over robotic movement for encoding behavior (Tai et al., 2004) and children learn new behaviors better from humans than from robots or androids (robots that look like humans) (Moriguchi et al., 2010a,b). The special effectiveness of social stimuli was recently shown when superimposing familiar face images onto the P300 Speller character matrix for ERP-based BCI performance increased accuracy and speed in healthy individuals (Kaufmann et al., 2011) and patients (Kaufmann et al., 2013).

Social Neurophysiology

Neurophysiological effects of social context and stimuli are distributed throughout the nervous system. Multiple areas of the brain respond to social conditions as assessed by a variety of methods, including transcranial magnetic stimulation, functional magnetic resonance imaging, electrophysiology, and molecular studies. To comprehensively describe all the neurological findings is not possible here so only a few are highlighted (see for reviews: Beer and Ochsner, 2006; Adolphs, 2009). The anterior cingular cortex (ACC) integrates complex stimuli, empathy, and decision making (Lavin et al., 2013). The striatum is a vital area for social interaction and reward (Báez-Mendoza and Schultz, 2013). In the inferior fronto-parietal areas, the mirror neuron system (discussed further below) is essential for social learning (reviewed in Rizzolatti and Sinigaglia, 2010). Differences in genetic expression are seen when zebra finches, a social songbird, sing to females directly rather than singing undirected song (Jarvis et al., 1998). Social behavior induces neurogenesis in the adult hippocampus in rodents (Gheusi et al., 2009; Lieberwirth and Wang, 2014; Peretto and Paredes, 2014). The early findings that social enrichment improves cognitive performance, neuronal growth, and overall brain mass (reviewed by Rosenzweig, 2007) followed by decades of confirmation, has led to the now standard practice that animals in research programs are provided appropriate social interactions (Guide for the Care and Use of Laboratory Animals, 2011). Conversely, decades of research have shown social stress during early development results in a number of behavioral and neurochemical deficits in multiple brain areas. For example, social isolation during rearing impairs neurogenesis in the dentate gyrus of the mouse hippocampus as revealed by deficits in spatial memory task (Ibi et al., 2008), and cell proliferation, cell survival, and neuronal differentiation are negatively affected by isolation during adulthood in female prairie voles (Lieberwirth and Wang, 2012).

Cognitive Function

Continuing development of BCIs that treat neurological and psychiatric disorders involving cognitive and emotional impairments suggests the need for the most comprehensive techniques to facilitate success. The research reviewed above clearly shows that cognition is changed by the qualities of social exchanges or social cues. For example, executive function can be increased (Ybarra et al., 2008) or reduced (Richeson et al., 2005) depending on the type of social interaction and even the identity of the actor. Where an individual falls along the continuum of social isolation (e.g., neglect, exclusion) to social connection has important consequences for cognitive abilities. In older adults, correlations between perceived isolation and poor cognitive responses have been shown (Tilvis et al., 2004; Wilson et al., 2007; Dickinson et al., 2011). In fact, brain and behavioral responses differ depending on the specific feeling of isolation/connection to the person with whom one is interacting (Cacioppo and Cacioppo, 2012).

Learning Socially

The social environment can arguably be said to be the richest environment for learning the most complex cognitive skills, pointing out the importance of training methods. A special quality about live social interaction is that it acutely primes the induction of novel responses (Gottlieb, 1991). For example, juvenile sparrows will learn the songs of another species when demonstrated by a live tutor that they do not learn from tape recordings (Baptista and Petrinovich, 1984). The use of social reinforcement has been noted to be particularly useful to improve BCI integration (reviewed in Lotte et al., 2013). Even if social feedback is provided by an android, behavioral change is better than when a computer display provides factual feedback (Ham and Midden, 2014). This suggests that when biofeedback systems are used (e.g., EEG, fMRI, MEG), engaging a person who communicates feedback in addition to computer displays could facilitate acceptance and speed of acquisition during training.

An essential learning substrate lies within the mirror neurons found in the cortical areas in humans; these neurons fire when observing or imitating another's behavior, evoking in the recipient the representational state of the observer's action or emotion (Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010). This allows mere observation of an action to increase motor memory encoding (Stefan et al., 2005; Celnik et al., 2006). Methods in stroke rehabilitation based on the mirror neuron system—action observation, motor imagery, and imitation—take advantage of this opportunity to rebuild motor function (Garrison et al., 2010). Similarly,

action observation has been proposed to interact with motor training in neurorehabilitation (Pomeroy et al., 2005), suggesting that cognitive training may also be possible by capitalizing on these mechanisms. For example, in a study with older adults, the combination of physical training and action observation together elicited encoding whereas conditions with only physical training or action observation failed. It is therefore suggested that employing a person who demonstrates the same action as the patient during BCI training would facilitate an increase in encoding more than just using imagery.

Brain-to-brain Coupling

Complex joint behaviors such as communication and social coordination depend on synchronous interactions. Interpersonal synchrony promotes a variety of positive outcomes, including affiliation, liking, rapport, and emotional support satisfaction. It is challenging to measure brain activity simultaneously from two people, but studies that examine inter-person variables such as synchrony have found revealing results using neuroimaging methods (summarized by Konvalinka and Roepstorff, 2012). Inter-personal entrainment of behavior between people occurs when engaged in rhythmic behavior, such as finger-tapping (Konvalinka et al., 2010) or chair-rocking (Richardson et al., 2007) resulting in unintentional coordination. Inducing synchronous activity induces brain-to-brain coupling, which might increase the efficiency of partnerships engaged with BCI use. Indeed, it has been suggested that our joint cognition with other minds increases their efficiency as a unit, particularly when in compromised situations (Wegner et al., 1991). Intriguing results with a multiuser BCI video game based on motor imagery showed improved utility, effectiveness, and engagement (Bonnet et al., 2013), suggesting methods using interacting brains would help reduce BCI illiteracy.

Brain-to-brain Transfer

Perhaps the most outstanding example of social interaction effect is the demonstration of brain-to-brain transfer of information via computer. In a recent study, the neural firing pattern code of a rat performing a memory task was transferred to a recipient rat, who then responded correctly more often than when stimulated with a random code or without stimulation (Deadwyler et al., 2013). Further, a study revealed that sensory information from a rat transmitted via computer included bidirectional reward contingency information that changed behavior of both donor and a naïve recipient rat in a location thousands of miles away (Pais-Vieira et al., 2013). Even human brain to rat brain transfer has been achieved (Yoo et al., 2013). These examples suggest that the day when neural signals can be transmitted between individuals is not out of the realm of possibility.

Recommendations

BCIs used for neurological rehabilitation require progressive practice with feedback and reward (Dobkin, 2007); here I suggest that capitalizing on social factors will result in better outcomes. The social environment provides a context particularly relevant for fostering the development and change of cognition. Given that the presence of social factors facilitates learning suggests that attention should be given to the conditions by which the BCI is integrated. For example, engage a loved one or a trusted facilitator who can supply emotionally rewarding feedback in training and treatment protocols. Use rewards of social stimuli, such as images of people or positive language, to enhance training, and deliver rewards with people instead of only computer displays. Pay attention to the emotional environment to ensure it is conducive for promoting change. Be aware that socially isolated patients will be more sensitive to negative cues and stimuli. Capitalize on the processes of imitation and action observation to stimulate responses of the mirror neuron system; in other words, have the patient and facilitator do the same task. Even if the patient is unable to perform the task, mere observation can stimulate motor neuron responses. Employ synchronization tasks between the facilitator and patient to increase trust and brain coupling. Finally, most revolutionary, use healthy individuals as donors to stimulate the patient via inter-brain coupling with brain-to-brain interfaces. In conclusion, just as it is essential that BCI development and use rely on the accurate use of technical principles, it is vital not to overlook the value of applying findings from social neuroscience in order to maximize the effectiveness of BCI implementation and integration.

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Impact of Short Social Training on Prosocial Behaviors: An fMRI Study

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Efficient brain–computer interfaces (BCIs) are in need of knowledge about the human brain and how it interacts, plays games, and socializes with other brains. A breakthrough can be achieved by revealing the microfoundations of sociality, an additional component of the utility function reflecting the value of contributing to group success derived from social identity. Building upon our previous behavioral work, we conduct a series of functional magnetic resonance imaging (fMRI) experiments ($N = 10$ in the Pilot Study and $N = 15$ in the Main Study) to measure whether and how sociality alters the functional activation of and connectivity between specific systems in the brain. The overarching hypothesis of this study is that sociality, even in a minimal form, serves as a natural mechanism of sustainable cooperation by fostering interaction between brain regions associated with social cognition and those related to value calculation. We use group-based manipulations to induce varying levels of sociality and compare behavior in two social dilemmas: Prisoner's Dilemma and variations of Ultimatum Game. We find that activation of the right inferior frontal gyrus, a region previously associated with cognitive control and modulation of the valuation system, is correlated with activity in the medial prefrontal cortex (mPFC) to a greater degree when participants make economic decisions in a game with an acquaintance, high sociality condition, compared to a game with a random individual, low sociality condition. These initial results suggest a specific biological mechanism through which sociality facilitates cooperation, fairness and provision of public goods at the cost of individual gain. Future research should examine neural dynamics in the brain during the computation of utility in the context of strategic games that involve social interaction for a larger sample of subjects.

Keywords: prosocial actions, sociality, value calculation, social cognition, BCI

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INTRODUCTION

Daily life confronts us with social situations and interactions on a regular basis. Thus, economic decisions are often embedded in a social context. However, we rarely think of how the brain processes the decisions we make, especially those decisions that affect the outcomes of other people with our decisions. Social factors such as group membership and affiliation motives have powerful effects on a range of behaviors, suggesting that these factors carry substantial decision utility for people. However, this "social utility" is rarely included in the formal models of economic behavior. This paper triangulates the theories of human social behavior from social psychology, decision modeling techniques from behavioral economics, and brain-imaging tools from neuroscience to draw a more precise picture of the mechanisms by which social factors influence economic decisions.

Recent efforts to unite these traditions have proven fruitful in delivering theoretical insights and a model-based precision to the study of economic behavior in a realistic social context (Akerlof and Kranton, 2000, 2010; Perc and Szolnoki, 2010; Perc et al., 2013; Lukinova et al., 2014; Berkman et al., 2015). One behavioral study (Berkman et al., 2015) confirmed that socialization induces prosocial behavior in economic games due to sociality. Participants are introduced in groups creating group differentiation, which easily satisfies the minimal group requirement (Tajfel, 1978). In line with Social Identity Theory we assert some esteem or value is gained by boosting the group (or derogating the outgroup; Tajfel and Turner, 1979) and, in turn, this additional value (Lukinova et al., 2014) plays a decisive role in encouraging prosocial actions. Building upon results of our behavioral work, we now report on a series of functional magnetic resonance imaging (fMRI) experiments that utilize the fMRI technology in combination with socialization and well-known economic games to measure whether and how sociality alters the functional activation of and connectivity between the social cognition network and the valuation network in the brain.

We use experiments in fMRI and laboratory facilities in an attempt to study the neural mechanisms of human social interactions and the microfoundations of prosocial behavior. The main novelty and contribution of this paper is in the reality of social interactions as opposed to artificial social interactions and in the combination of two social dilemmas in the fMRI study. To our knowledge the Prisoner's Dilemma (PD) and various representations (sequential vs. simultaneous; matrix vs. a game tree) of Ultimatum Game (UG) have not appeared together in prior neuroeconomics research. Our study follows pioneer fMRI studies that compare PD to other games (e.g., Stag Hunt; Emonds et al., 2011, 2012). Besides regular UG we use Welfare Game (WG), a novel 2×2 simultaneous version of UG that preserves the distributional essence of the game, as well as its antecedent, the UG.

Using fMRI gives us a unique perspective on how sociality works. We examine neural dynamics in specific systems when people compute their utility in the context of strategic games that involve various levels of social interaction. Social science researchers use neuroimaging as the key tool to understand the nature of the various peculiar aspects of human behavior such as "economic irrationality" (Peterson, 2005), altruism and "altruistic punishment" (De Quervain et al., 2004; Waytz et al., 2012), asymmetry between gains and losses (Yacubian et al., 2006), cooperation (Fett et al., 2014; Watanabe et al., 2014), preference of egalitarian outcomes (Sanfey et al., 2003; Tricomi et al., 2010; Dawes et al., 2012; Yamagishi et al., 2012; Osinsky et al., 2013), decision about an unfair split (Güroğlu et al., 2014), and theory of mind (Lee and Harris, 2015; Strombach et al., 2015). If social neuroscience (Cacioppo et al., 2002; Norman et al., 2012) attempts to understand mechanisms that underlie social behavior using a mix of biological and social approaches (Willingham and Dunn, 2003), neuroeconomics opens up the "black box" of the brain by finding neural correlates of choice behavior (Camerer et al., 2005; Lohrenz and Montague, 2008; Glimcher and Fehr, 2013; Lampert et al., 2014; Schroeder and Graziano, 2015) and behavior under risk and uncertainty (Hsu et al., 2005). Unfortunately, current knowledge of neural mechanisms in prosocial decision making is still limited (Fehr and Camerer, 2007; Lee, 2008; Emonds et al., 2011, 2012, 2014; Declerck et al., 2013; Declerck and Boone, 2015; Kuss et al., 2015).

For the purposes of this paper, sociality, or social utility, is defined as an additional component of the utility function reflecting the value of contributing to group success derived from social identity, defined as knowledge, value, and emotional significance for group membership (Tajfel, 1982). In economic terms, social identity may be one of the mechanisms by which sociality comes to have a positive decision utility. There are many ways of manipulating sociality for the purpose of testing its effect on economic decisions and the associated neural systems. To our knowledge, a formal typology of the various kinds of sociality is not currently available, even though such a typology would be quite useful for the present line of research and related efforts. In the course of our behavioral research, we surveyed the relevant literature and identified two broad classes of social manipulations (Low sociality and High sociality). We follow on this distinction in our fMRI study. In particular, during our Pilot fMRI Study we compare playing with humans to playing with computers, whereas in the main study we focus on the difference between the behavior in economic games where the opponent is a random individual or an acquaintance.

We have specific, *a priori* hypotheses about the likely brain regions involved in each of the two target processes (sociality and valuation). A growing body of work implicates the ventral striatal dopamine circuit in the integration and calculation of subjective value or utility, including the ventromedial prefrontal cortex (vmPFC), the ventral aspects of the caudate (vC), and the nucleus accumbens (nAcc; Plassmann et al., 2007; Hare et al., 2008; Ruff and Fehr, 2014). Social cognition, on the other hand reliably recruits activation in a network of brain regions including the dorsomedial prefrontal cortex (dmPFC), the posterior cingulate cortex (PCC), and the temporoparietal junction (TPJ; Amodio and Frith, 2006; Van Overwalle, 2009). Pertinent to the present research, a recent study found that activity in TPJ tracked perceived social distance between an actor and a target, and interacted with the vmPFC, a region involved in value calculation, to modulate the actor's decisions about how to divide up a fixed pot of money to be shared by the actor and the target (Strombach et al., 2015). This study provides proof-of-concept that social cognition regions can interact with valuation regions to influence economic decisions. Existent reviews in neuroeconomics add another neural network that is consistently recruited when people face social dilemmas, i.e., network related to cognitive control (Declerck et al., 2013). Thus, one can formulate a competing hypothesis: the interaction of cognitive control and valuation regions of the brain facilitate prosocial decision making.

Since our experimental design includes two types of economic games we can also examine the question of whether the neural bases of social welfare choices are different from those of collective action. The regions of the brain associated with reward and valuation are under our focus and we hypothesize that these

brain regions should be more active during the fair condition than during the unfair condition in the UG. Indeed, the vmPFC is reported to activate during tasks involving inequality in social settings (Fliessbach et al., 2007; Tabibnia et al., 2008; Tricomi et al., 2010; Aoki et al., 2015). Inequality is noticed by participant once reward comparison between the other and herself is accomplished. However, it also hurts when she realizes that she falls behind. We hypothesize that there will be an increased activity in the reward associated brain regions (vmPFC) as well as the brain regions critical for processing emotions, such as amygdala and OFC (Davidson et al., 2000; Dolan, 2002) in variations of UG condition as opposed to the PD game condition.

A more precise understanding of the mechanisms by which sociality affects economic decisions in a collective action situation is the essential next step in improving social brain–computer interfaces (BCIs; Sexton, 2015).

MATERIALS AND METHODS

All participants are recruited through advertisements on campus. All subjects are right handed, healthy, have normal or corrected-to-normal vision, have no history of psychiatric diagnoses, neurological or metabolic illnesses, and are not taking medications that can interfere with the performance of fMRI. Participants can be of any gender and ethnicity, but must be at least 18 years old. The only exclusion criterion is based on MRI safety screening (ferromagnetic metal in the body, e.g., dental braces). The participants in the fMRI experiment can earn $5 just for showing up on the day of experiment and up to $20 more, depending on their decisions throughout the game. During all game conditions the participants earned a number of points that was later transferred to money. Subjects provide written informed consent approved by the University of Oregon Human Studies Committee.

On the day of experiment, four people are invited to the conference room in Lewis Center for neuroimaging (LCNI) that is adjacent to the scanning suite. Thus, in every experiment one participant for the fMRI experiment is paired with three other subjects for the reality of the high sociality conditions: Human and Acquaintance. Before they participate in economic games the subjects have time to get to know each other and engage in an informal conversation, i.e., undergo socialization, the technique adopted from our behavioral research (Berkman et al., 2015). Specifically, the participants are asked to introduce themselves by name to the others and say one exciting thing about themselves. The participants then embark on a 10-min interaction with the goal of creating a list of five attributes they all have in common to report back to the experimenter. Finally, one of the participants is asked to go to the scanning room for fMRI experiment and remaining three participants stay in the conference room and proceed with a computer experiment.

Computer experiment laboratory data ($N = 75$) are collected with the help of the z-Tree (Zurich Toolbox for Readymade Economic Experiments) software package (Fischbacher, 2007). The stimuli presentation is identical to the fMRI experiment, with one row chooser and two column choosers (one of the column choosers plays against a predetermined computer strategy).

Pilot Study

Subjects of the fMRI experiment are 10 UO college students (five females). Stimuli include two sociality conditions (human and computer opponents), two game conditions (PD and WGs), a feedback screen that shows profit of participant based on her decision, and a control condition.

The PD payoff matrix is formed around (1, 2, 4, 6; **Table 1**) values. When one participant defects and the other cooperates, then defector gets the maximum value – 6, and the cooperator receives the minimum payoff of 1. If both cooperate, participants get four each, whereas if both defect, they get two each.

The WG is a novel game not seen in prior research. It resembles a simultaneous version of the UG with an option for an unfair offer. The UG is a game often played in laboratory experiments in which two players interact to decide how to divide a sum of money that is given to them. One of the players proposes how to divide the sum between the two players, and the other can either accept or reject this proposal. If the second player rejects the proposal, none of the players receive anything. However, if the second player accepts, the money is split according to the proposal. Usually the game is played only once or with a randomly chosen partner so that reciprocation is not an issue. For the same reason, players do not change roles within one game. The equilibrium in the UG is not in the favor of the second player. By rejecting the proposal, the second is choosing nothing rather than something. So, for a rational player it would be better to accept any proposal that gives any amount bigger than 0. Contrary to the economic theory of self-interest, multiple studies (Henrich, 2004; Oosterbeek et al., 2004) show that in many cultures people offer (50:50) splits and offers less than 20% are usually rejected.

The WG's payoff structure corresponds to values in PD (1, 2, 4, 6; **Table 1**) Based on the payoffs the row chooser always prefers to choose up. The column chooser's best response to the row chooser's dominant strategy is to choose left. That is why the Nash equilibrium is (2; 6). However, the row chooser always gets a worse payoff than the column chooser. So, if the row chooser prefers egalitarian outcomes, the row player's deviation from the equilibrium can occur and result in either of the two egalitarian options: (1; 1) and (4; 4).

Prior to entering the scanner the subjects complete a series of practice trials of a similar game on paper. This ensures that the

TABLE 1 | Prisoner's dilemma (PD) and Welfare game (WG) payoffs.

	PD			Welfare Game	
	L	R		L	R
U	4, 4	1, 6	U	2, 6	6, 2
D	6, 1	2, 2	D	1, 1	4, 4

PD and WG payoffs are presented in the matrix form. One of the players chooses between rows, i.e., between up (U) and down (D). The other player (randomly paired) chooses between columns, i.e., between left (L) and right (R).

participants understand and are ready for the stimuli presented in the actual experiment. Participants are told on the day of experiment that they will be Row choosers [choosing between up (U) and down (D)] and will maintain the same role for the whole experiment. Subjects are instructed to look at the central plus sign, and had to switch their attention from the central plus sign to the game stimulus (a table 2 × 2 that is centered on the central plus sign) in each trial to determine the their response by pressing either left or right button on the button box in their right hand. Subjects know that by pressing the left button, they choose up (U) and by pressing the right button – down (D). This study uses deception. Participants are told that their opponents in the high sociality condition are humans. In reality, the participant in the fMRI study always plays a computerized strategy with fixed probabilities: for PD game, right (R) with $p = 0.85$, left (L) with $p = 0.15$; for WG, L with $p = 0.85$, R with $p = 0.15$. Feedback collected following the experiment indicates that the deception was effective and that subjects believed that their opponents were human.

In order to answer the research questions the following neural experimental design is used. The experiment consisted of four blocks [Humans + PD (PG1), Humans + WG (PG2), Computers + PD (CG1), Computers + WG (CG2)] with events within each block. To distinguish between blocks the instruction screen in the beginning of each block indicates whether the participant will play a computer or a human. The game condition does not change throughout the block. The blocks are alternated: for half of the participants the order is PG1, PG2, CG1, CG2, for the other half – CG1, CG2, PG1, PG2. We use an event-related fMRI design with a pseudorandom (predetermined unpredictable) order of game and control condition within a block with the same interstimulus and intertrial intervals used in M. Posner attention studies (Flombaum and Posner, 2005; Abdullaev et al., 2010) that approximate an exponential distribution with a certain mean. The jittering of the time intervals between game and feedback and between feedback and the next trial is done in order to separate brain activity to the game and feedback stimuli.

In the game condition (**Figure 1**), the plus sign remains on the center of the screen for 1000 ms. The game stimulus follows after a variable interval ("one of 12 predetermined intervals including three 300 ms intervals, and one each of 550, 800, 1050, 1550, 2300, 3300, 4800, 6550, and 11800 ms, approximating an exponential distribution with a mean interval of 2800 ms;" Abdullaev et al., 2010). The game stimulus stays until response or for 30000 ms. Then a fixation screen is on for 1000 ms followed by another variable intertrial interval (mean of 6000 ms) and finally the feedback screen is on for 2000 ms till the onset of the next trial.

In the control condition, the plus sign remains on the center of the screen for 1000 ms. The control stimulus (each cell in **Figure 1** 2 × 2 table is replaced with "X, X") follows after a variable interval (mean of 2800 ms). The control stimulus stays until response or for 5000 ms. As in the game condition, then fixation screen is on for 1000 ms followed by another variable intertrial interval (mean of 6000 ms) till the onset of the next trial. Four blocks are presented, and each block has 30 trials (20 game condition trials and 10 control condition trials) with a different pseudorandom order of conditions and intervals.

Responses are recorded with two buttons on an MRI-compatible button box. Reaction times (RT) are measured from the game stimulus to the button press. The control trial is constructed in order to isolate the mechanical activity of the finger pressing on the button box. We expected that with each button press, we should see the ipsilateral cerebellum and the contralateral primary motor cortex activation. Also there is a 30 s baseline period in front of each block with no stimuli except a central plus sign for fixation. So that each condition of the task can be compared to the baseline period.

fMRI stimuli are presented for the participant in the MRI scanner and behavioral data are collected using the Presentation program[1] run on a computer. Stimuli are presented with a digital projector/reverse screen display system to the screen at the back end of the MRI scanner bore. Subjects see the screen via a small tilted mirror attached to the birdcage coil in front of their eyes.

Imaging is performed using a 3T Siemens Allegra head-only MRI scanner at Lewis Center for Neuroimaging. A standard birdcage coil is used to acquire data from the entire brain. Subjects wear earplugs and earphones to protect their hearing. Additional soft padding is used between earphones and inside the wall of the head coil to diminish head movements.

For functional MRI, the EP2D-BOLD (Blood oxygen level dependent) sequence is run with repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, Field of View (FOV) = 200 mm. The brain is covered with 32 4 mm thick slices acquired in a custom manner (first even slices and then odd slices). For structural MRI scan, the 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) TR = 2500 ms, TE = 4.3 8ms, flip angle = 8°, FOV = 256, 160 slices is run for 8 min to acquire 1 mm^3 high resolution anatomical scans for registration purposes.

Main Study

Subjects of the fMRI experiment are 15 individuals recruited from the Eugene, OR community, college-aged (eight females). The procedures are nearly identical to the Pilot Study, except for the sociality, game conditions, and fMRI acquisition. Stimuli include two within-subject opponent conditions, Low sociality (Random Individual), and High sociality (Acquaintance), and two within-subject game conditions, PD, UG as responder. Thus, each trial falls into one of four cells, with participants playing anonymously against either someone from the Eugene community who the participant has not met or someone from the socialized group, and playing the PD game, or the UG game as responder. This study uses deception. Although participants believe they are playing with real people (according to participants' feedback), the opponent in all three games is in reality a computer that follows the Nash equilibrium strategy with random noise to reduce suspicion. Following the game phase of each trial, participants are shown a feedback screen displaying the profit the

[1] www.neurobehavioralsystems.com

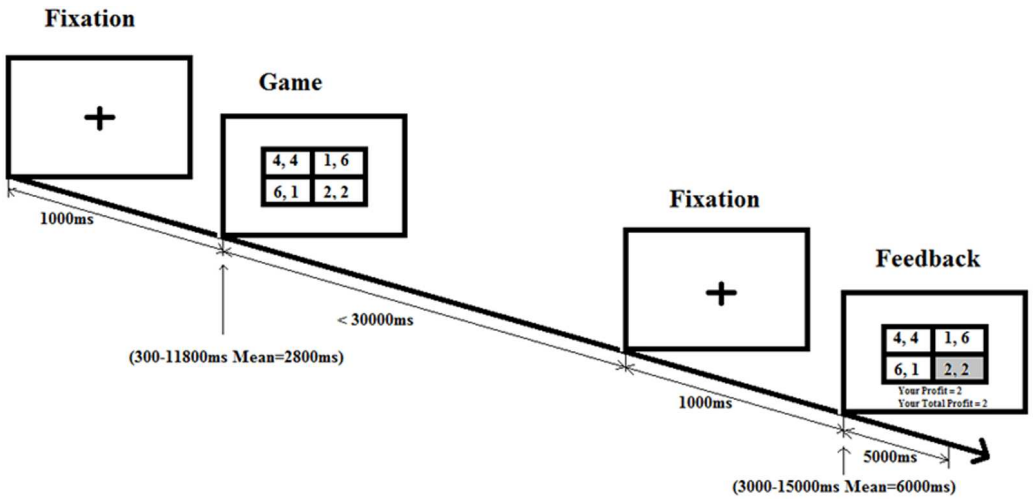

FIGURE 1 | Game condition schedule. Following the fixation cross, there is a game phase for each trial, where participants need to make a choice in a social dilemma. After pressing on the button box, participants are shown a feedback screen displaying the profit the participants earn based on their decision and the decision of their partner.

participant earned based on their decision and the decision of the partner.

Therefore, the experiment consists of four blocks (Acquaintance + PD, Acquaintance + Ultimatum, Random Individual + PD, Random Individual + Ultimatum) with 30 trials within each block (20 experimental and 10 control trials). To distinguish between blocks the instruction screen in the beginning of each block specifies, whether the participant would play against a person from his/her Socialized group (Acquaintance) or against a Random Individual.

The PD game payoffs are the same as in Pilot Study (**Table 1**). The UG is modeled in such a way that a participant always chooses between two options, either accept an unfair offer that corresponds to up (U) or reject the offer pressing down (D). Equally likely are offered (2; 6) and (3; 5) splits, where the lesser value is an offer to a participant.

MR scans are acquired in the Siemens Skyra 3 Tesla scanner at LCNI, a research-dedicated, whole-body system optimized for functional brain imaging. Participants are situated in the scanner by one of LCNI's imaging technicians, who also control the scanner during the session. Experimental stimuli (e.g., images, instructions) are presented using a magnet-compatible, rear-projection system controlled by a PC using Presentation Software. Participant responses (e.g., up/down decisions) are collected on a 10-key button box (only two buttons are used) capable of recording responses to the millisecond level. A shimming protocol maximizes homogeneity in the field, and a 30 s, T2*-weighted scout allows slice prescriptions for all subsequent scans. We acquire a high-resolution anatomical T1-weighted MP-RAGE scan (TR/TE = 2300/2.1 ms, 192 × 192 matrix, 1 mm thick, 160 sagittal slices, FOV = 256), functional images with a T2*-weighted echo-planar scan (33 axial slices, TR/TE = 2000/30 ms, 90-deg flip, 64 × 64 matrix, 4 mm thick, FOV = 200), and in-plane gradient echo field map magnitude and phase images to correct for inhomogeneities in the magnetic field (33 axial slices, TR/TE = 345/8.06 ms, 40-deg flip, 64 × 64 matrix, 4 mm thick, FOV = 200).

Analysis

The epochs used for the analysis are from the game stimulus onset until response.

FSL Procedures

The Pilot Study is first analyzed using General Linear Modeling (GLM) as implemented in the FSL 5.0.2 (FMRIB Software Library). fMRI data is analyzed using FEAT (FMRIB Expert Analysis Tool) available as part of FSL[2] (Smith et al., 2004). Preprocessing includes the default options, such as separating images of brain from the rest of the images of the head, i.e., creating a brain mask, using the Brain Extraction Tool (BET; Smith, 2002), pre-whitening for local autocorrelation correction using FILM (FMRIB Improved Linear Model; Woolrich et al., 2001), motion correction based on rigid-body transformations using MCFLIRT (Motion Correction FMRIB Linear Image Registration Tool; Jenkinson et al., 2002), spatial smoothing using a Gaussian kernel and highpass temporal filtering as implemented in FSL as well as slice timing correction using a customized text file.

The analysis is done in three steps. On the first level we analyze each session's data, i.e., execute time-series analysis of the raw 4D fMRI data. We generate voxel-wise parameter estimates of the hemodynamic (blood-oxygen-level-dependent) responses to the different stimuli we used in the fMRI experiment. These voxel-wise parameter estimates represent the change in the blood-oxygenation level for a given stimulus compared to the baseline neural activation of no stimulus presentation and control stimulus. Modeled regressors include cooperation, i.e., choosing up (U) in PD game both in the human and computer

[2]www.fmrib.ox.ac.uk/fsl

conditions, C_PG1 and C_CG1, respectively; defection, D_PG1 and D_CG1; inequity aversion [down (D) in WG], IA_PG2 and IA_CG2; and inequity tolerance, IT_PG2 and IT_CG2. Each explanatory variable is created by convolving the stimulus actual duration times (from onset of stimulus till response using one of the buttons) within each stimulus with a standard gamma hemodynamic response function using FEAT. Through first-level analysis, we obtain parameter estimates as well as statistical maps for each regressor.

On the second level we combine each subject's activation across several blocks and create contrasts (for human vs. computer conditions: C_PG1 vs. C_CG1, D_PG1 vs. D_CG1, IA_PG2 vs. IA_CG2, IT_PG2 vs. IT_CG2; and WF vs. PD: IA_PG2 vs. C_PG1) using a fixed effects analysis with cluster-level statistical threshold of $Z > 2.3$ and $p < 0.05$. In order to compare human condition to computer condition and inequity aversion in WG to cooperation in PD we subtract one stimulus type (e.g., in Low sociality condition) from another type (e.g., in High sociality condition). The hypothesis of interest here is whether in each voxel the activation to human condition stimuli is greater than in computer condition. We also implement this type of contrast in the opposite direction, i.e., where activation in computer condition is higher than activation in human condition. In result, we generate statistical maps for each of the five contrasts for each subject. These contrast activation maps are registered to each subject's own high-resolution structural image and also to the Montreal Neurological Institute (MNI) 152-standard template.

Finally on the third level, we use FLAME (FMRIB's Local Analysis of Mixed Effects) modeling and one-sample *t*-test to decide whether the group activates on average. Mixed effects model the subject variability and, therefore, allow making inferences about the wider population from which the subjects are drawn. Each of the contrasts for the group are Gaussianized intro *Z*-statistical images and thresholded at $Z > 2.3$ with a cluster-corrected significance threshold of $p < 0.05$ (Worsley, 2001). The high resolution structural MRI images of individual subjects are standardized to the MNI space and averaged within the group to create an average structural template.

SPM 12 Procedures

The Main Study is analyzed using identical procedures in SPM12 (Wellcome Department of Cognitive Neurology, London, UK[3]), which includes correction for field inhomogeneities, realignment, and coregistration of functional images to each subject's own high-resolution structural image using a six-parameter rigid body transformation model, reorientation to the plane containing the anterior and posterior commissures, spatial normalization into space compatible with an MNI atlas, and smoothing using a 6 mm^3 FWHM Gaussian kernel. Statistical analyses are implemented in SPM12. For each participant, event-related condition effects are estimated according to the general linear model, using a canonical hemodynamic response function, high-pass filtering (128 s), and a first-order autoregressive error structure. At the individual level, BOLD signal is modeled in a fixed effects analysis with separate regressors modeling each condition of interest during the game presentation period, for the decision making, and feedback periods. Linear contrasts are created for each comparison of interest (e.g., PD + High Sociality vs. UG + High Sociality, PD + Low Sociality vs. UG + Low Sociality, PD + High Sociality vs. PD + Low Sociality, and UG + High Sociality vs. UG + Low Sociality). These contrasts are then imported to group-level random effects analyses for inference to the population. The above-threshold activations table (shown at $P < 0.05$, FWE) is created with WFU_pickatlas[4]. The particular regions reported in the results are visualized using xjView toolbox[5].

PPI in AFNI

Psychophysiological interaction (PPI) analysis is conducted in AFNI[6]. We define the seed region as medial PFC (defined using the Harvard–Oxford structural atlas[7]). The PPI analysis identifies regions showing differential coupling with the mPFC during High Sociality vs. Low Sociality conditions. The mPFC ROI is projected from MNI space to individual subject space, the time series data are extracted from the combined left and right mPFC, and terms associated with the baseline, linear drift, and head motion are removed. These cleaned time series data are deconvolved with an assumed gamma impulse response function, and then multiplied by the High Sociality vs. Low Sociality condition contrast to generate an interaction term. An additional GLM is implemented as before, but with additional regressors corresponding to the deconvolved mPFC time series, the High Sociality vs. Low Sociality condition contrast, and the interaction of these two regressors, which is the key term in the PPI analysis. This final interaction regressor is used to identify brain regions in which functional coupling with the mPFC differs during the interaction with an Acquaintance compared to Random Individual. Beta weights corresponding to this interaction regressor are converted to *Z*-scores to allow for between-subject comparison.

RESULTS

Behavioral Results

In the PD the trend is typical, with high (moderate) levels of cooperation in the first few rounds devolving into consistent moderate (high) levels of defection. The only difference is witnessed between high sociality (humans, acquaintances) and low sociality (computers, random individuals) conditions (**Table 2**). Playing acquaintances in the Main Study resulted in slightly higher levels of cooperation than those in the Pilot Study for Humans condition. Nevertheless, we observe significant difference between cooperation rates in the PD in the Pilot Study

[3]www.fil.ion.ucl.ac.uk/spm/

[4]http://www.nitrc.org/projects/wfu_pickatlas/

[5]http://www.alivelearn.net/xjview

[6]http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html

[7]http://www.cma.mgh.harvard.edu/

TABLE 2 | Computer experiment behavioral results.

Pilot study conditions	Cooperation in PD	Inequity tolerance in WG	Main study conditions	Cooperation in PD	Inequity tolerance in UG
Human	28%	30%	Acquaintance	49%	76%
Computer	16%	46%	Random individual	18%	66%

Behavioral results of computer experiments for Pilot and Main studies are reported. The percentages of cooperative decisions (choose U or L in the PD) and the frequency of inequity tolerance decisions (choose U in the WG or accepted an unfair offer in the UG) across studies and conditions are listed.

TABLE 3 | fMRI experiment behavioral results.

Pilot study conditions	Cooperation in PD	Inequity tolerance in WG	Main study conditions	Cooperation in PD	Inequity tolerance in UG
Human	26%	40%	Acquaintance	34%	71%
Computer	15%	62%	Random individual	21%	51%

Behavioral results of fMRI experiments for Pilot and Main studies are reported.

(Humans vs. Computers, $N = 30$, p-value $= 0.002$, t-test) and in the Main Study (Acquaintances vs. Random Individuals, $N = 45$, p-value $= 0.0006$, t-test).

Results of the Computer Experiment for Welfare and UGs are puzzling. Whereas for WG the egalitarian outcome (inequity aversion), rather than Nash equilibrium (2; 6) is more likely, for the UG accepting unfair offers (inequity tolerance) is predominant. The difference between sociality conditions is not significant.

For the fMRI portion of the experiment the same pattern remains: rates of cooperation are significantly higher for the high sociality condition than those for the low sociality condition (**Table 3**; Pilot Study: Humans vs. Computers, $N = 10$, p-value $= 0.001$, t-test; Main Study: Acquaintances vs. Random Individuals, $N = 15$, p-value $= 0.02$, t-test). It is important to notice that the cooperation level averages oscillated around the mean till the very last round due to the persistent tests of cooperative strategy by participants that face nasty Nash equilibrium computerized strategy.

We observe significant difference between sociality conditions, for the Welfare and UG (Pilot Study: Humans vs. Computers, $N = 10$, p-value $= 0.05$, t-test; Main Study: Acquaintances vs. Random Individuals, $N = 15$, p-value $= 0.05$, t-test). The directions of the effect are distinct: acceptance of unfair offers is higher for Computers (low sociality) compared to Humans (high sociality) conditions, but is lower for Random Individual (low sociality) compared to Acquaintance (high sociality) conditions, similar to what is seen in the Computer Experiment. The WG is a simultaneous game, whereas the UG is sequential. In the UG the subject accepts or rejects the offer that is presented to her. In the WG she does not know what will be offered, so it is not necessarily inequity aversion, but might be as well risk aversion. In other words in WG the subject provides a hedge against potential inequity by forcing the egalitarian outcome, whereas in the UG it is not possible without losing everything. That is why in UG most of the subjects tolerate inequity.

fMRI Results, Pilot Study

The fMRI analysis of the Pilot Study in FSL focuses on the functional activity pattern associated with social domain and economic games participants play. We determine areas in the brain where the neural activation is higher for subjects playing with humans, than playing with computers in completing several different tasks. We report functional activation in the areas as specified in MNI structural atlas (Mazziotta et al., 2001; Collins et al., 2004) and Talairach Daemon Labels atlas (Lancaster et al., 2000).

Cooperation in the PD game with humans compared to cooperation in PD with computers is associated with a signal increase in dorsolateral prefrontal cortex (DLPFC), Brodmann areas (BA) 8 and 9 (Cooperation contrast: BA 8 [$x = 69$, $y = 69$, $z = 55$ (MNI_152 space coordinates)], Z-score $= 3.01467$). Whereas BA 9 functions include sustaining attention and working memory, BA 8 is even more intriguing, as it is linked to the management of uncertainty (Platt and Huettel, 2008) as well as hopes or high expectations. Many studies see DLPFC as a contributor to rational decision-making in social situations. Although cooperation in the PD game is seen by many as irrational, the theory of sociality (Lukinova et al., 2014; Berkman et al., 2015) provides a rational explanation for such behavior by adding an economic component to the subject's utility function in the social context. Thus, activation in the Cooperation contrast can be attributed to another demonstration of sociality at work, where brain processes cooperation as a rational decision.

Contrast between WG and PD game displays highlight in BA 30 [$x = 36$, $y = 45$, $z = 33$ (MNI_152 space coordinates), Z-score $= 2.55405$] that along with adjacent areas forms posterior cingulate gyrus. Its functions include spatial memory and orientation (Owen et al., 1996), as well as face recognition (Leube et al., 2001). Neither the former, nor the latter directly correspond to the stimuli presented to the subjects. BA 39 [$x = 61$, $y = 33$, $z = 51$ (MNI_152 space coordinates), Z-score $= 2.54531$], located at the middle temporal gyrus, is also involved in calculation (Grabner et al., 2007), as well as in "theory of mind" (Goel et al., 1995), i.e., modeling knowledge, rationality, etc., of another person's mind. Indeed, calculation and "theory of mind" occur in both games (Rilling et al., 2004), however, while the PD game is familiar and is frequently used in multiple courses in college, the WG, as a rare simultaneous version of UG, requires participants to think

TABLE 4 | Above-threshold activations (shown at $P < 0.05$, FWE) are presented for the contrasts of interest.

Contrast	Anatomical region	Coordinates (*x, y, z*)	*T*-statistic	*Z*-statistic	Cluster size
PD > UG					
	L inferior frontal gyrus	(−38, 3, 34)	11.49	4.87	2
	L inferior parietal lobule	(−41, −44, 58)	10.5	4.72	1
UG > PD					
	R superior frontal gyrus	(21, 49, −18)	12.49	4.8	2
High sociality > Low sociality					
	L sub-gyral	(−35, −38, 38)	11.08	4.81	1
	L superior frontal gyrus	(−10, 12, 58)	10.63	4.74	1
	R inferior semi-lunar lobule	(12, −60, −52)	9.28	5.15	6
	L pre-central gyrus	(−36, −12, 58)	8.87	5.07	10
	L post-central gyrus	(−40, −36, 64)	8.81	5.05	7
	R cingulate gyrus	(−42, −24, 40)	8.27	4.91	3
	R superior temporal gyrus	(50, 20, −18)	7.87	4.79	1
Low sociality > High sociality					
	L inferior parietal lobule	(−35, −47, 46)	13.66	5.16	6
	L inferior parietal lobule	(−35, −56, 46)	13.16	5.09	4
	L inferior frontal gyrus	(−50, 9, 34)	13	5.07	2
	L precuneus	(−7, −62, 54)	11.02	4.8	1
	R precuneus	(3, −56, 54)	10.94	4.79	2
	R cingulate gyrus	(18, −38, 38)	8.83	5.06	1
	R parahippocampal gyrus	(38, −22, −18)	8.58	4.99	1

MNI_152 space coordinates are reported.

through other subject's strategy and execute the cost-benefit analysis.

fMRI Results, Main Study

The analysis of neuroimaging data in SPM focuses on the functional activity pattern between games and opponent conditions (**Table 4**; shown at $P < 0.05$, FWE).

One of the goals is to determine brain areas where neural activation is higher in one game or another. In Pilot Study, when participant plays in a PD Game compared to her making decisions in a WG besides significant clusters already identified, activation is higher in vmPFC, Brodmann area 32 (BA 32, $x = 5.70$, $y = 25.53$, $z = 34.81$; T-statistic $= 6.0101$). It is likely that brain activation differences between games, namely WG and UGs, are mainly due to calculation issues and the novelty of WG to college students. It is vital that BA 32 associated with rational thought processes does not appear to be more activated, when comparing PD and UG in the Main Study.

When comparing cooperation decision in PD to acceptance of unfair offers in the UG or agreement to Nash equilibrium in the WG, no significant clusters are found. We assert that in the social setting the neural basis for tolerability to defection (opponent's strategy in PD is nasty) and tolerability to inequity (advantageous position of column chooser in WG and unfair offer in UG) is identical, representing confrontation with the social world that is at times unjust and rough.

Besides the BA 8 and BA 9 activations already identified in the Pilot Study differences between sociality conditions in PD also show higher activations in orbitofrontal area, BA 11 ($x = -28.80$, $y = 50.61$, $z = -9.89$, T-statistic $= 6.0101$; **Figure 2**), known for its connection to planning, reasoning, and decision making. Cooperation in high sociality condition is indeed attributed to a well-planned and a reasonable, if not rational decision. The contrasts between High sociality and Low sociality involve among others the following brain activations: Superior

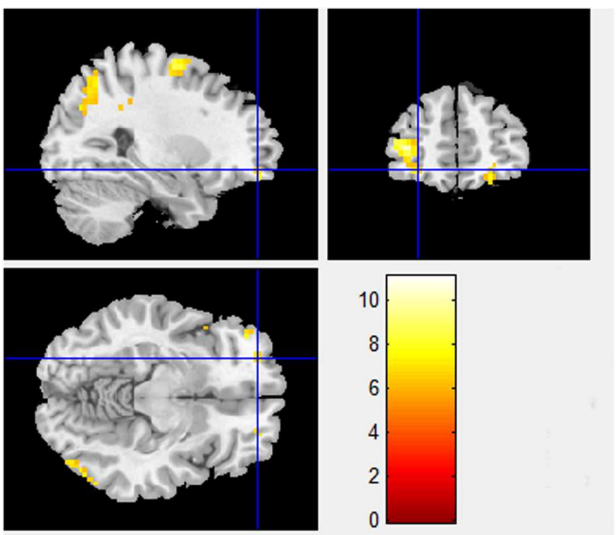

FIGURE 2 | High sociality > Low sociality contrast (BA 11). Contrast between High sociality and low sociality conditions reveals activations in orbitofrontal area, BA 11 ($x = -28.80$, $y = 50.61$, $z = -9.89$). This area is associated with planning, reasoning, and decision making in general.

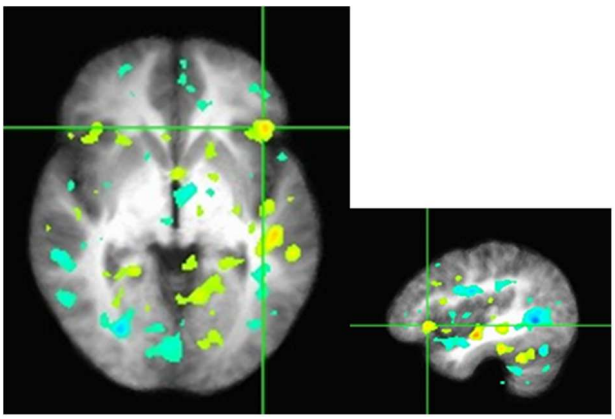

FIGURE 3 | *Z*-scores from the seed to the inferior frontal gyrus in the axial and sagittal views. Functional connectivity of mPFC with the right inferior frontal gyrus, a region previously associated with cognitive control and modulation of the valuation system. Regions depicted are found to correlate with mPFC to a greater degree when participants make economic decisions as they interacted with others in the high sociality condition compared to the low sociality condition.

Frontal Gyri, Inferior Frontal Gyrus, Anterior Cingulate, and Parahippocampal Gyrus.

We conduct preliminary connectivity tests using PPI analysis using the mPFC as a seed, a brain region associated with valuation. The software used for obtaining the activations is Analysis of Functional Neuro-Images (AFNI). The presence of a positive context-dependent interaction in a region (i.e., a PPI) can be interpreted as greater relative connectivity between that region and the seed in one condition compared to another. In this case, the regions depicted in **Figure 3** are found to correlate with mPFC to a greater degree when participants made decision in PD as they interacted with others in the high sociality condition compared to the low sociality condition. **Table 5** shows the correlation coefficients for the areas of interest, i.e., the areas highlighted for the High > Low Sociality contrast.

Several regions emerge that have previously been implicated in prosocial economic choice (e.g., the right inferior frontal gyrus and the DLPFC; Tabibnia et al., 2008). Notably, these regions modulate activation of the valuation system in cases when self-control is necessary to override impulsive or habitual choices such as selfish economic decisions (Hare et al., 2008). Several small peaks also emerge in the valuation network proper (not shown), but the small sample size prevents strong inferences based on these data.

TABLE 5 | R coefficients with seeded ROI in the medial frontal gyrus (coefficient range −0.0019445 to 0.01676).

	AFNI-r coefficient	# of voxels	% max coefficient
Fusiform gyrus	0.006777	1492	0.4043
Inferior frontal gyrus	0.006322	731	0.3772
Insula	0.006274	509	0.3743
Anterior cingulate	0.006351	381	0.3789
Parahippocampal gyrus	0.005702	306	0.3402

Regions that were significantly positively correlated with medial prefrontal cortex (mPFC) to a greater degree when participants made economic decisions as they interacted with others in the high sociality condition compared to the low sociality condition: r refers to the Pearson correlation coefficient relating neural activity in that cluster and mPFC activation coefficients at the group level.

DISCUSSION

If social cognition constantly results in a different pattern of brain activity than a non-social one and the regions of brain activation during social cognition have a special status (high levels of activity even at rest) in the brain (Adolphs, 2003; Jenkins and Mitchell, 2011), to what extent are brain systems that control social behavior domain specific (Cosmides and Tooby, 1994; Stone et al., 2007)? If evolutionary perspective provides theoretical grounding for domain specificity, neuroscience then gives an opportunity to investigate it.

This paper focuses on the comparison of two sociality conditions. It is the first attempt to find what brain regions correspond to a neural value of sociality and lay a foundation to identify and estimate this neural value. The key is to induce prosocial behaviors in economic games, different in nature, but common in representation. Our findings support the theory of sociality. Indeed, we assert that additional social utility is calculated in the human brain, when a person interacts with someone from the socialized group she identifies herself with. This additional social utility may cause prosocial decisions, such as cooperation in the PD, and may as well appear rational to the brain. A good way of talking about sociality is by illustrating what happens when it is impaired (Edmiston et al., 2015): sociality can be described as the opposite of autism.

Based on our research we propose that economic games, such as PD representing collective action and the UG, the simplest demonstration of bargaining, can be intertwined. We observed that presenting UG and PD together results in higher cooperation rates than when participants deal with the PD only. One explanation is a spillover effect produced during the UG. In the social environment, norms of fairness in the UG may encourage us to be as well fair in the PD, i.e., cooperate. Recent findings, however, do not report any correlation between rejecting unfair offers and prosocial behaviors in other games (Yamagishi et al., 2012). The fact that we did not observe significant differences in activations between the games could be due to highly perplexed cognitive processes involved in these social dilemmas when sociality is induced.

The data collected from the fMRI experiments can serve to answer many more questions, than those raised in this paper. For example, how do subjects perceive outcomes? While in this study, our main focus is on the stimuli from onset till response, next we can take into account the reaction toward the outcome displayed to the participant. How will participants react to unfairness or defection? Or how will participants react and what brain activation will be related to it if they defect, while the opponent cooperated? Why do dopaminergic and subcortical regions show

no activation in the task? These research questions: to identify the brain regions that are sensitive to sociality and to test the relative effectiveness of the sociality inductions in altering neural activation in the social cognition and valuation networks and economic decisions – hold promise to advance the social aspects of BCI (Sexton, 2015).

AUTHOR CONTRIBUTIONS

All authors designed the experiments; EL carried out the experiments, programmed the software for the experiment, prepared the data, and conducted the analysis; EL wrote the paper; all authors reviewed the paper and the results.

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OPINION
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The Elephant in the Mirror: Bridging the Brain's Explanatory Gap of Consciousness

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INTRODUCTION

The successes of the artificial retina and cochlea have lent encouragement to researchers in the general field of brain augmentation (Gantz et al., 2005; Dagnelie, 2012). However, in order for brain augmentation to progress beyond conventional sensory substitution to comprehensive augmentation of the human brain, we believe a better understanding of self-awareness and consciousness must be obtained, even if the "hard" problem of consciousness (Chalmers, 2007) remains elusive. Here we propose that forthcoming brain augmentation studies should insistently include investigations of its potential effects on self-awareness and consciousness. As a first step, it's imperative for comprehensive augmentation to include interfacing with the biological brain in a manner that either distinguishes self (biological brain) from other (augmentation circuitry), or incorporates both biological and electronic aspects into an integrated understanding of the meaning of self. This distinction poses not only psychological and physiological issues regarding the discrepancy of self and other, but raises ethical and philosophical issues when the brain augmentation is capable of introducing thoughts, emotions, memories and beliefs in such an integrated fashion that the wearer of such technology cannot distinguish his biological thoughts from thoughts introduced by the brain augmentation.

A consideration of self begins with the conventional mirror self-recognition test (MSR) (Gallop, 1970) that has been successfully executed with Eurasian magpies (Prior et al., 2008), bottlenose dolphins (Reiss and Marino, 2001), orca whales (Delfour and Marten, 2001), human infants typically between 18 and 24 months (Amsterdam, 1972; Rochat, 2003), and notably the Asian elephant (Plotnik et al., 2006). The only primate species reported to pass the Gallup Mirror Test, albeit controversially, were orangutans and chimpanzees (Suárez and Gallup, 1981). For years, MSR has been the designated litmus test for determining whether a species possesses self-awareness (SA), ultimately raising the question of whether the animal is then a conscious entity as a result of passing this test (De Veer and van den Bos, 1999). "Mirror self-recognition is an indicator of self-awareness," proclaims Gallup et al. (2002). If indeed so, then the subsequent query to raise is whether self-awareness, the ability to differentiate oneself among others, is a precursor to or derivative of consciousness, and whether the mirror test is necessary and sufficient (Morin, 2011).

In light of brain research like the Blue Brain Project (Markram, 2006), BRAIN Initiative (Kandel et al., 2013), and development of neural prosthetics, the interest in consciousness is steadily growing. Here, we not only encourage the study of and suggest methods for addressing science's "*elephant in the room*," which asserts consciousness is neither physical nor functional, but also place the *Elephas maximus* in our proverbial mirror to obtain a perspective toward forming a cohesive alliance between philosophical studies of consciousness and neural engineering's augmentative innovations. As MSR is purposed to grant the animal subject personal physical inspection from

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an objective viewpoint, resulting in self-cognizance, so shall we take the approach to examine our modern scientific methods in conceptual mirrors, to appraise our consciousness dilemma and propose an assertion for progression in augmentative technologies. Following here is a succinct primer of consciousness and SA. We also issue a proposition as to how brain augmentation can influence the arrival of machine consciousness. Overall, we state our opinion for (1) why SA must be systematically examined in conjunction with brain augmentation approaches and (2) how such a merger could become a tool for investigating consciousness.

Ineffable Consciousness

The first pitfall encountered with consciousness is the inability to derive a functional explanation for what it means to *experience*. Chalmers (2007) lists the "easy" problems of consciousness as "the ability to discriminate, categorize, and react to environmental stimuli; the integration of information by a cognitive system; the reportability of mental states; the ability of a system to access its own internal states; the focus of attention; the deliberate control of behavior; the difference between wakefulness and sleep." These phenomena are relatively feasible to exploit and can be described in computational model terms and neural operation derivations. Chalmers then counteracts them with the "hard" problem of lacking competency to explain why and how we have phenomenal experiences when being entertained by a movie, exhibiting a sensation toward classical music, or having feelings when watching a sunset. Explaining how the brain processes visual and auditory signals is trivial in comparison to how those same signals translate to *qualia*, subjective phenomenal experiences.

Explanatory Gap Dilemma

The term *explanatory gap*, coined by philosopher Joseph Levine (1983), notes our inability to connect physiological functions with psychological experience, thus creating the *gap*. Although Levine synonymizes consciousness with subjective feelings, the explanatory gap additionally alludes to reasoning, desires, memory, perception, beliefs, emotion, intentions, and human behavior/action. Correlating physical brain substrates to thoughts and feelings is the base of dispute between two parties: materialist reductionists and non-reductionists (Sawyer, 2002). Materialists' chief view, representative of most neuroengineers, on the matter involves the belief that "when the brain shuts off, the mind shuts off" and the brain is the sole causative driver for consciousness. However, non-reductionists (typically philosophers) embrace a holism approach of mandating that the brain's cortical components are insufficient in capturing consciousness, undertaking the possibility of supernatural properties. It's an inquiry of necessity and sufficiency. The brain may be necessary for mental functions, but is it sufficient? Earlier analytical inspections on conscious experience have implied that an exclusive reductive justification is not satisfactory in delineating its emergence (Churchland, 1988; Kim, 2005; Clayton, 2006; Feinberg, 2012). A novel approach is needed to explain such experience. Our explanatory gap needs an explanatory bridge.

UNRAVELING SELF-AWARENESS TOWARD AUGMENTATION

Although many facets of consciousness are difficult to investigate, the development of objective tests for SA could be utilized for brain augmented technologies. With SA comes the sense of *agency*. Agency imparts a sense of who is the owner of an action/trait, the self, and who represents any entities excluding self, the other(s). Self-other dichotomy processing in the brain is essential to consciousness due to the necessary implications the embodiment of "self" must have to form body ownership. Once an agent gains the ability to discern when its own body is the source of sensory perceptions, it will form body awareness that entails proprioceptive information. We can look to working experiments that attempt to showcase how the brain augments the "self" when necessary to complete a task (**Figure 1**). Perceptual parametric information builds a premeditated awareness of (1) body part locations and (2) the manipulation of those same parts in space. Body awareness was demonstrated by a machine via Gold and Scassellati (2007) who built a robot named Nico that successfully distinguished its own "self" from "other." Nico observably achieved self-recognition by completing mirror-aided tasks expending inverse kinematics. Nevertheless, it's believed Nico lacked consciousness.

Before the sense of agency becomes fully refined through experiences over time, there must be a repertoire built for perceptions and actions. Whether, action and perception are interdependent or each fundamentally isolated has been the focus of another ongoing debate. It's not yet concretely understood how the representation of self is formed during the initial stages of life. Either an agent first uses perception to motivate their

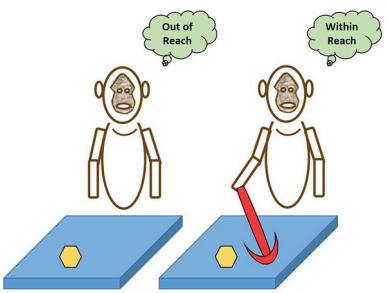

FIGURE 1 | Extension of self-representation. Here are two depictions of macaque monkeys that exhibit a case of the body making use of tools as an extension of the "self." If given a task to retrieve an object (yellow hexagonal shape) that is outside the peripersonal space and the immediate reach of an extended limb (left macaque), the body relies on its physical limitations to define the "self" and its aptitude for success of the task. However, when an apparatus is introduced (right macaque) that can help achieve the task's goal, the brain's neural correlates are able to augment themselves to psychophysically merge tools that were formerly considered to be of "other" classification into the "self" body schematic and permit optimal behavioral actions to take place (Hihara et al., 2006; Carlson et al., 2010). The paradigm for "self" is malleable to accept the dynamic interplay necessary to achieve an aim for biological function that was once previously unattainable. As tool-use changes the brain's representations of the body and alters proprioception, we subsequently believe it parallels how enriched brain augmentation can alter an individual's self-awareness and consciousness.

actions in the world or it first directs their actions to help drive perception of the sensory world or both occur simultaneously. In either method bodily awareness is eventually acquired which contributes to defining subjective cognitive attributes. Two opposing views attempt to solve this problem: the action-oriented theory of visual perception, which suggests that perception results from sensorimotor dynamics in an *acting* observer (Gibson, 1966; Noë, 2004; Mandik, 2005), and the dual-visual systems hypothesis, which advocates independent streams of perception and action (Schneider, 1969; Goodale and Milner, 1992; Jacob and Jeannerod, 2003; Milner and Goodale, 2006). Self-awareness uses expectation of impending perceptions and actions to gauge the assimilation of inner experience and external reality. Building a self-aware framework in augmentative technologies requires integration of an *expectancy intuition*, which is the capability to critique on the basis of differences between reality and internal experience. This is our tactic for creating systems with faculties for using perception and action to make predictions of self-sensory states, become self-adaptable to new environmental stimuli, and set objectives for self-improvement.

Crucial for understanding agency is determining how the embodied senses fuse to form self-referential experience (Fingelkurts et al., 2016a,b). It's our opinion that future advances of brain augmentation hinges on the application of such knowledge. Once we bridge this gap of the unknown we'll be challenged to use computational intelligence to create consciousness artificially and to integrate synthetic qualia with that produced in the brain. Presently, artificial devices can create various aspects of consciousness. Artificial perception is made available via cochlear, retinal, and tactile implants. But they simply work alone as replacements for sensory organs with consciousness and SA arriving later in the brain's neural processing. Applications for augmenting consciousness would contribute to studies relating to emotions, attention, supplementing memory capacity, personality alteration, experience enrichment, sensory perception enhancement, and hypernormal brain plasticity for self-repair.

PROPOSED TRANSITION TO MACHINE CONSCIOUSNESS

The marvel of human intelligence is its ability to eclipse physical limitations and overcome our biological constraints to form an ever-evolving existence (Jerison, 1973). One primary goal for reverse-engineering the human brain is to recreate the same functional mechanisms that underlie human consciousness in our software infrastructures, neurorobotic agents, and computational systems. However, prosthetic memory, sensory implants, neurofeedback (EEG Biofeedback) and brain computer interfaces (BCIs) are all working examples of fusing such "intelligent" systems with the brain, leading to conceivable prospects for consciousness-altering devices. Although BCIs commonly target disability treatments and brain function recovery from lesion, the amalgamation of computational devices with the cortical brain itself (Fingelkurts et al., 2012) may even prompt increasing developments of an operational "exobrain" (Bonaci et al., 2014) for the purposes of better understanding how our brain works. For example, in a scenario where a split-brain condition is present within a subject, we now have the option to look toward interfacing artificial exobrains with the cerebrum; such an interface can either serve as a replacement for neurological issues or supplement features the brain does not naturally comprise. If these exobrains have a modicum of manipulability, then we can explore the plausibility of mind transfer from device to organ and vice versa; thus, providing speculation for a conscious machine that can affect how we can perceive, act, express emotion, feel, and adapt. This poses ethical concerns as it opens the door for alterations of an individual's SA when augmentation is capable of modifying reasoning skills and subjective judgment. Successful augmentation of the sort might render the individual powerless in discriminating actual characteristics and thoughts from those that are mock and introduced artificially outside the cortex. Combining the precision and information processing speed of a computer with the intrinsic non-computational attributes of a human may provoke discoveries of the mind (e.g., consciousness) that we as humans are currently incapable of resolving. We suggest efforts made toward an augmentative interface between brain and machine that prompts the human mind to think beyond its unknown limits for the construction of our explanatory bridge.

CHALLENGES MOVING FORWARD

Many people view an in-depth exploration into consciousness and its emergence as a gamble, considering decades already spent on the matter with a void of consensus (Dennett, 1991; Jibu and Yasue, 1995; Hameroff and Penrose, 1996; Stapp, 2001; Crick and Koch, 2003; Tononi, 2008; De Sousa, 2013; Seager, 2016). Before we attempt to create another hypothesis, our approach needs to change; it's our suggestion to further refine the constructs and emergence of SA and to use brain augmentation as an instrument for inspection. We need to define an objective test for determining whether an entity is a sentient being. This test in addition to advances in neural engineering provide optimism that disputes within the consciousness field can be resolved. Augmentation has a promising future as an enhancement to our brains and will hopefully influence our centuries-old methods of thinking about consciousness toward an answer for science's greatest mystery.

AUTHOR CONTRIBUTIONS

JB: This author was responsible for providing the overall opinion of the topic and crafting the outline of the article. JB contributed most of the text and references supplied in the document. JB also primarily conducted the necessary research to develop this article. JB supplied the latter sections of the text with original ideas to add to the discussion of the Brain Augmentation research topic. AP: This author assisted in crafting the thesis of the article and provided additional topic of discussion to implement within the text. AP provided introductory material for the article and also made revisions to each section to ensure a coherent message about our opinion was made. AP also restructured the format of the article to enhance comprehension to an audience with varying backgrounds.

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Problems with theories that equate consciousness with information or information processing

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Attempts to augment the function of the human brain inevitably involve in some way what Block (1995) calls phenomenal consciousness—bodily sensations and perceptual experiences—the redness of a strawberry, the smell of newly-baked bread. At present there is no consensus among scientists about what such sensory experiences are. This Opinion piece points out some problems with one of the major theatrical viewpoints on that question.

CLASSIFICATION OF THEORIES OF CONSCIOUSNESS

The oldest classification system has two major categories, dualist and monist. Dualist theories equate consciousness with abstracta. Monist (aka physicalist) theories equate it with concreta. The Stanford Encyclopedia of Philosophy approaches the task of defining abstracta and concreta by the ancient method of providing examples and letting the reader work it out for themselves: it says "Some clear cases of abstracta are classes, propositions, concepts, the letter 'A', and Dante's Inferno. Some clear cases of concreta are stars, protons, electromagnetic fields, the chalk tokens of the letter 'A' written on a certain blackboard, and James Joyce's copy of Dante's Inferno."

A more recent classification (Atkinson et al., 2000) divides theories of consciousness into process theories and vehicle theories: it says "Process theories assume that consciousness depends on certain functional or relational properties of representational vehicles, namely, the computations in which those vehicles engage. On this view, representational contents are conscious when their vehicles have some privileged computational status, independently of any particular intrinsic property of those vehicles. What counts is 'what representational vehicles do, rather than what they are'…For vehicle theories, on the other hand, consciousness is determined by intrinsic properties of representational vehicles, independently of any computations in which those vehicles engage."

The relative number of words devoted to process and vehicle theories in this description hints that at present, process theories massively dominate the theoretical landscape. But how sensible are they really?

THEORIES THAT EQUATE CONSCIOUSNESS WITH INFORMATION OR INFORMATION PROCESSING ARE DUALIST

Most process theories identify consciousness with the processing of information. As Velmans (1991) puts it: "For radical behaviorists, all talk of mind could be translated, without scientific loss, into talk about behavior. For the new 'radical cognitivists' all talk of mind (including consciousness) can be translated, without scientific loss, into talk about information processing." In the quarter century since 1991, process theories have become so deeply embedded that the term "radical" no longer applies. Pretty well all cognitive scientists, computationalists and psychologists now think of consciousness in terms of information processing. Indeed, among these groups the information processing paradigm is so prevalent that it is usually not seen as necessary to state it explicitly.

Perhaps as a consequence, it is not widely recognized that the concepts "process," "information," and "information processing" are all abstracta. Thus, mapping the new process/vehicle dichotomy onto the old dualist/physicalist axis reveals that process theories (in the sense of theories that equate consciousness with information or information processing *per se*, rather than with any particular physical realization or implementation thereof) are dualist. Philosopher David Chalmers is one of the few process theorists to recognize that his theory is an example of what he calls "naturalistic dualism" (Chalmers, 1996). The word "naturalistic" may have been included in this description in an attempt to make the "dualism" part more acceptable to cognitive scientists, most of whom prefer to see themselves as staunchly scientific physicalists.

CHALMERS' PROCESS THEORY

Chalmers (1996) takes information theory (Shannon, 1948) as his starting point, but immediately generalizes Shannon's two-state "bit" of information to the concept of a multi-state "information space," defined as an abstract space consisting of a number of information states and a structure of "difference relations" between them. Chalmers then discusses ways in which information states can be realized physically, mentioning thermostats, books, telephone lines, and Bateson's catchy slogan about information's being "a difference that makes a difference," before proposing as a fundamental principle that "information (in the actual world) has two aspects, a physical and a phenomenal aspect" (Chalmers, 1996, p. 286). On this theory then, information

actually *is*—has the property of being—conscious.

One immediate problem with this idea is that it involves a radical redefinition of the word information, slipped in by the back door in the sense that Chalmers never acknowledges that everyone else's definitions are specifically at odds with his.

There are several technical definitions of information, which differ slightly depending on the field of enquiry. In information philosophy, Floridi (2005) says " 'information' is often used to refer to non-mental, user-independent, declarative semantic contents, embedded in physical implementations like databases, encyclopedias, web sites, television programmes and so on…the *Cambridge Dictionary of Philosophy,* for example, defines information thus: 'an objective (mind independent) entity…Information can be encoded and transmitted, but the information would exist independently of its encoding or transmission'." Floridi then lists a number of sources that define information as data + meaning, before arguing that truth is also a necessary ingredient (because if information is not truthful, it should more properly be called misinformation or pseudo-information). Other technical definitions exclude even meaning. Classical or Shannon information theory was born out of a need to address the technical problems experienced by Shannon's employer Bell Labs in extracting signals from noise in telephone and telegraph lines, so Shannon (1948) equates information simply with the observation that a particular one out of a defined set of possible messages has been sent from one entity to another—the meaning of the message is explicitly stated to be irrelevant. Cybernetics (Sayre, 1976) later generalizes Shannon's definition to equate information with increased probability, or reduction in uncertainty.

The point is that all of these definitions take information itself as an objective, *mind-independent* entity. Thus, whatever it is for which Chalmers (1996) and others now claim a subjective or phenomenal aspect, it cannot be what everyone else calls "information."

A second objection to the Chalmers proposal, which this time he does acknowledge, is that thermostats (for example) clearly carry information, but are not widely regarded as having any degree of consciousness. Chalmers offers a choice of two options to deal with this:

(1) Perhaps only some *kinds* of "physically realized information spaces" are conscious.
(2) Perhaps thermostats are conscious.

Chalmers himself chooses option (2). He suggests, on no particular grounds, that the level of organization at which consciousness "winks out" might be lower than a thermostat but higher than a rock.

TONONI'S PROCESS THEORY

Another widely cited process theorist is Giulio Tononi. Tononi prefers Chalmers' option (1)—his integrated information theory (IIT) proposes that only *integrated* information is conscious. Actually the initial formulation of IIT (Tononi, 2004) sidesteps the question altogether, saying only: "The theory presented here claims that consciousness *has to do with* the capacity to integrate information" and "To recapitulate, the theory claims that consciousness *corresponds to* the capacity to integrate information." [emphases added]. But this unobjectionable formulation soon morphs into the firm statement "consciousness is integrated information" (Tononi, 2008, 2012). Integrated information is defined in terms of various brain processes known to be associated with consciousness—one might almost infer that it was tempting simply to equate integrated information with conscious information, except that this would not have been terribly informative in the cybernetic sense of the word—and both Tononi and Seth et al. (2011) invest considerable effort in suggesting how integrated information might be quantified. Later Koch (2014) adds Chalmers' option (2) to the IIT mix and invokes panpsychism, admitting that inasmuch as integrated information is everywhere, consciousness must also be everywhere. Despite all the work that has by now been put into mathematical quantification of integrated information, no specific estimate of the quantity necessary for the appearance of consciousness is offered, but Koch speculates that the internet might be conscious.

MCFADDEN'S PROCESS THEORY

McFadden (2013) in his CEMI (conscious electromagnetic information) theory, sticks with Chalmers' option (1), proposing that consciousness is associated only with *electromagnetically encoded* information. McFadden draws a distinction between extrinsic information (which he says is symbolic and arbitrary and exemplified by Shannon information) and intrinsic information, (which "preserves structural aspects of the represented object and thereby maintains some gestalt properties of the represented object"). He argues that "to avoid the necessity of a decoding homunculus, conscious meaning must be encoded intrinsically—as gestalt information—in the brain." The precise relationship of this encoded gestalt information to consciousness is never spelled out, but it is probably not identity. McFadden does ascribe properties to consciousness and as he rightly says in his discussion of Chalmers' dual aspect theory, "it is not at all clear whether it is legitimate to ascribe properties to abstractions, such as the informational content of matter."

WHAT'S THE PROBLEM?

There are several problems with all of this. First, since information is explicitly defined by everyone *except* process theorists as an objective entity, it is not clear how process theorists can reasonably claim either that information in general, or that any subset or variety of information in particular, is subjective. No entity can logically be both mind-independent and the very essence of mind. Therefore, when process theorists use the word "information" they must be talking about something quite different from what everyone else means by that word. Exactly what they are talking about needs clarification.

Second, since information is specifically defined by everybody (including Chalmers) as an abstract entity, any particular physical realization of information does not count as information at all. A "physical realization of an information space" like James Joyce's copy of Dante's Inferno may *carry* information, but it is not itself information—it's just an arrangement of paper and ink. A "physical realization of an information space" like Joe Bloggs' brain when he looks at

an octopus may *encode* information, but it is not itself information—it's just an arrangement of neurons, glia and ions. Of course, it is certainly possible to claim that particular arrangements of neurons, glia and ions *are* conscious—indeed some remarkably eminent people have done so. But that claim no longer represents a dualist/process theory. It now represents a physicalist/vehicle theory. Since at least Chalmers specifically identifies his theory as dualist, it is far from clear how he (or others) can claim even information status, never mind consciousness, for any particular kind of "physically realized information space."

Third, it is a problem at least for scientists that process theories are untestable. The hypothesis that a particular brain process *correlates with* consciousness can certainly be tested empirically. But the only potentially testable prediction of theories that claim *identity* between consciousness and a particular kind of information or information processing is that this kind of information or information processing will be conscious no matter how it is physically instantiated. This is a feature of process theories that makes them very attractive to those who would like to build a conscious artifact out of hardware. The unspoken prediction is that all one has to do to create artificial consciousness is emulate the computations done by the brain in some manner—any physical instantiation will do. But suppose it were possible to build a piece of hardware that adequately reproduced the brain computations underlying a particular sensory experience. How could we know whether the result was conscious? Consciousness is such a private phenomenon that nobody can be 100% sure even that their human neighbors are conscious at any given moment. We know *we* are conscious. Other humans look and act more or less like us, so when they tell us they have a particular conscious experience, we give them the benefit of the doubt. But what about a bit of hardware? Even a novice software writer could produce a piece of code that typed "I feel hot" whenever a thermostat registered a high temperature, but not many people would believe the appearance of this message meant the thermostat was experiencing hotness. Hence, neither the idea that information or information processing is conscious, nor its logical extension panpsychism (the idea that everything is conscious), is in any obvious way testable.

Of course, that doesn't necessarily mean these ideas are untrue. It just means they are unscientific. It may be fine for philosophers to play with the idea that thermostats and computer networks are conscious, but scientists are usually constrained to dealing in testable hypotheses.

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Ethical issues with brain-computer interfaces

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INTRODUCTION

Brain-computer interfaces (BCIs), or brain-machine interfaces (BMIs) involve real-time direct connections between the brain and a computer (Kubler, 2009; Wolpaw and Wolpaw, 2011). Bidirectional feedback between the user and the system produces physical changes that can restore some degree of motor or communicative control for individuals with lost limbs, extensive paralysis or who are significantly neurologically compromised (Hochberg et al., 2006, 2012). In these respects, a BCI can enable an individual with severe brain or bodily injury to regain some degree of agency. By providing the subject with the relevant type of feedback, the device may enable her to translate an intention into an action despite the inability to perform voluntary bodily movements. There are two types of feedback with a BCI. The first concerns feedback about the outcome of a self-initiated, BCI-mediated action, such as moving a computer cursor or robotic arm. It provides only indirect feedback about brain activity. The second type concerns direct feedback about the level of brain activity itself. The first is more pertinent to the potential to restore some behavior control in the sense that one can perceive the success or failure of their mental act. Although it is still at an early stage of development, an EEG- or fMRI-based BCI might also enable minimally conscious individuals or those with complete locked-in syndrome to communicate wishes about medical treatment when they are unable to do this verbally or gesturally (Sellers, 2013). These applications of interface technology raise a number of ethical issues (McCullagh et al., 2014), three of which I will discuss in this article. First, in some cases patients' and caregivers' expectations about recovering motor function with a BCI might not be reasonable given the cognitive challenges in operating the system. This might result in psychological harm when the subject's desires and intentions to produce actions fail to be realized. Second, the different types of electrodes used to detect and respond to motor cortical neural signals involve different levels of invasiveness and different benefit-risk ratios that have to be weighed with a view to the probable success or failure of the technique. Third, the use of a BCI for communication in neurologically compromised patients prompts the question of whether their responses would be evidence of the capacity to make informed decisions about their care.

EXPECTATIONS

The user of a BCI can execute an intention to perform a motor task through changes in the system caused by electrodes detecting signals in, for instance, the motor cortex mediating the intention. Success in operating the system depends on a combination of unconscious operant conditioning of brain responses and conscious goal-directed expectation of the subject. These depend in turn on how effective the practitioner is in training the subject how to operate the system. As in other cases of traumatic brain injury, goal-directed thinking in some patients with tetraplegia may be impaired if there is significant damage to neural networks in frontal regions mediating planning and decision-making. This may also impair the subject's capacity to understand the benefits and risks of the technique and give informed consent to participate in BCI research and treatment (Hochberg and Cochrane, 2013).

Ordinarily, motor skills are performed unconsciously and automatically following an initial period of conscious attention and learning. For those with severe paralysis, however, sustained attention is required both while being trained to operate the interface and effectively operating it to execute motor tasks. Subjects whose cognitive capacity for planning has been impaired by injury to the central nervous system may have difficulty in translating their thoughts into actions or fail to do so. Failure to meet the expectation to produce certain actions may cause distress and harm in some subjects by defeating their interest in recovering some, albeit limited, degree of motor control. Planning is a critical component in moving a prosthetic limb, for example. The subject must indicate with his brain and mind where the limb should go before executing the intention to move it. The cognitive workload requires considerable time and effort. This may cause frustration and anxiety and increase the probability of failure for some in trying to achieve their goal. It can exacerbate the feeling of a loss of behavior control. To minimize the probability of harm, investigators and practitioners must educate users on the potential positive effects and limits of BCIs. They should also adopt strict selection criteria and include only those with largely preserved cognitive functions who could give informed consent and would more likely be trained to successfully operate it. This may seem unfair to those with impaired levels of cognition who lack these capacities. Nevertheless, the idea of providing equal opportunity for all paralyzed individuals to access to a BCI would have to be weighed against the potential for emotional harm if a subject cannot meet the

cognitive demands of operating the system and his expectations are not met. Discriminating on the basis of levels of cognitive function may be justified on these grounds.

BENEFITS AND RISKS

BCIs utilize wired or wireless systems to detect and allow transmission of signals in the motor cortex into actions. The significance of these systems for benefit and risk to patients depends not so much on the type used but their level of invasiveness. Theoretically, the distinction between wired and wireless systems is orthogonal to this level. The non-invasive type consists of scalp-based electrodes that are part of the equipment required to record EEG. Because they do not involve intracranial surgery and implantation of a device in the brain, they do not involve a risk of infection or hemorrhage. At the same time, though, they may not readily read signals from the motor cortex because the cranium can smear them.

In electrocorticography (ECoG), electrodes are implanted epidurally or subdurally (Leuthardt et al., 2004). These can decode motor cortical signals more readily than scalp-based electrodes because they are not susceptible to cranial smearing. But they entail some risk of infection and hemorrhage. Like the non-invasive system, both forms of ECoG BCIs impose constraints on the subjects' freedom from the wires running from the electrodes to the machine. Wireless systems consisting of a microelectrode array implanted in the motor cortex avoid this problem and are less burdensome for subjects. Because they can decode and transmit signals from this region more directly, implanted arrays are more likely to facilitate the execution of the subject's intentions in actions. Still, this would depend on the specifics of the neurological deficit and the patient's ability to manipulate the BCI. Moreover, in addition to the risk of infection and hemorrhage, microelectrode arrays raise the issue of biocompatibility between the implanted objects and surrounding neural tissue. The electrodes may reorganize and induce changes in the tissue. These changes may be salutary, especially if they promote neuroplasticity and the generation of new neuronal connections that could bypass the site of brain or spinal cord injury causing loss of motor function. But they could also cause adverse changes in the surrounding tissue and result in neurological and psychological sequelae. A safe and effective array that could function for many years would be one in which the surrounding neuropil grew into the electrode. This would be more stable and allow myelated axons to be recorded using implanted amplifiers (Kennedy et al., 2011). If this occurs, then invasive systems can be functionally superior to and as safe as non-invasive systems. The first type can have a more favorable benefit-risk ratio than the second.

COMMUNICATING WITH A BCI

EEG- and fMRI-based BCIs might enable individuals to reliably communicate when they are unable to communicate behaviorally (Birbaumer et al., 2008, 2014). This involves three distinct patient groups. Minimally conscious patients have residual awareness of self and surroundings. Locked-in patients are fully aware despite being almost completely paralyzed. Some of these patients can communicate through voluntary eyelid movements. These in turn are distinct from completely locked-in patients who lack the capacity for any voluntary bodily movements. Conscious perception and expression of intentions in locked-in patients is different from that of minimally conscious patients, and this may better facilitate communication through a BCI. One challenge for this intervention would be that BCIs typically utilize visual feedback, and minimally conscious and completely locked-in subjects have limited or no capacity to receive feedback from and respond to a visual stimulus in learning how to operate the system. Alternatively, tactile or auditory feedback could be used to enable communication (Kubler, 2009; Hochberg and Cudkowicz, 2014). Yet even if this modality could overcome the limitations associated with a lack of visual feedback, questions would remain about the meaning of "communicate." Specifically, it is not clear whether the responses of linguistically impaired minimally conscious or even fully conscious locked-in patients would be evidence of the cognitive and emotional capacity to give informed consent to continue or discontinue artificial hydration and nutrition (Brady Wagner, 2003; Jox, 2013).

Some investigators have claimed that fMRI-guided BCIs could enable minimally conscious patients with a high level of cognitive function to make these decisions (Peterson et al., 2013). But emotionally laden decisions about life-sustaining treatment reflect a person's values and attitudes about quality of life. It is questionable whether these values and attitudes can be expressed by simple "Yes" or "No" responses to questions (Monti et al., 2010), and yet they have to be included in any robust sense of "communication." This involves more than being aware, even fully aware. More sophisticated interface systems enabling the expression of complex semantic processing may or may not confirm that the patient had the requisite capacities. Hochberg and Cudkowicz point out that among completely locked-in patients there have been "no reports of restoring communication using a neural signal-based BCI in this most severely affected population" (Hochberg and Cudkowicz, 2014, p. 1852; Birbaumer et al., 2014). Moreover, Fernandez-Espejo and Owen acknowledge that, with current interface technology, simple affirmative or negative responses to questions about whether a minimally conscious patient wanted to continue living would not be sufficient to establish that the patient had the "cognitive and emotional capacity to make such a complex decision" (Fernandez-Espejo and Owen, 2013, p. 808). But they also say that "it is only a matter of time before all of these obstacles are overcome" (p. 808).

This last point may be overly optimistic. Even advanced BCIs that could detect neural activity correlating with complex semantic processing might not be sufficient to show that the subject had the cognitive and emotional capacity to make an informed and autonomous decision about life-sustaining treatment. Some form of behavioral interaction may be necessary to confirm that the subject had this capacity. Medical professionals and caregivers must be cautious not to read too much into BCI-enabled responses and interpret them as having a meaning they lack.

CONCLUSION

BCIs can benefit individuals by restoring varying degrees of motor control and possibly the ability to communicate. But

expectations of some subjects and their caregivers may exceed what they can reasonably achieve with the technology and result in psychological harm. Selecting candidates with higher levels of preserved cognitive function for BCI research and treatment and educating them on the potential benefits and limitations of the technique is advisable to prevent or at least minimize harm. The fact that a particular BCI system is more invasive than others does not imply that it has an unacceptable degree of risk and may instead indicate a more favorable benefit-risk ratio if it does more to enable the execution of intentions in actions and promote neuroplasticity. Perhaps the most significant application of BCIs would be in enabling minimally conscious or completely locked-in patients to communicate. Yet it is questionable that even the most sophisticated system alone could demonstrate that these subjects have the ability to clearly and meaningfully communicate their wishes and make informed decisions about life-sustaining treatment. Decision-making capacity falls along a continuum correlating with a continuum of cognitive and emotional capacities, and there is no algorithm providing a definitive answer to the question of where the threshold at which one has a sufficient degree of these capacities lies. All relevant parties need to be cautious and not infer that a BCI indicating certain levels of brain activity and semantic processing in a subject is evidence of an understanding of the ethical magnitude of life-and-death decisions and the ability to make them.

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Minds, motherboards, and money: futurism and realism in the neuroethics of BCI technologies

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INTRODUCTION

Brain computer interfaces (BCIs) are systems that enable the brain to send and receive information to and from a computer, bypassing the body's own efferent and afferent pathways. BCIs have been used in experimental animal models to augment perception, motor control and even memory (Velliste et al., 2008; Berger et al., 2011; Torab et al., 2011). Human BCIs include cochlear implants and a host of experimental devices including retinal implants (Niparko et al., 2010; Klauke et al., 2011). BCI technology holds the potential to benefit humanity greatly, but also the potential to do harm, and its ethical implications have therefore been addressed by a number of commentators.

THE PROBLEM WITH SCIENCE FICTION

Commonly addressed ethical challenges with BCIs concern a future when the technology is used to give people superhuman abilities, or to control their thoughts and desires. The idea of human beings with computer-augmented brains engenders a wide range of reactions from laypersons, mostly negative (Lipsman et al., 2009; Lebedev, 2014). There is revulsion toward these so-called cyborgs occupying the "uncanny valley" between fellow human and robot (Mori, 1970). Some fear being overtaken by cyborgs with superior perceptual, cognitive and motoric powers while others are afraid that BCIs imposed upon us would result in mind control. Still others foresee tremendous benefit for humanity, with BCI enhancements elevating individuals and society.

Positive or negative, these images of computer-augmented brains are as speculative as they are vivid. Therein lie two significant challenges for ethical analysis of BCIs. First, we have strong emotional reactions to the prospects of humans with cyborg brains. Second, our limited real-world experience with BCIs deprives our ethical analyses of a foundation of pragmatic empirical knowledge. As a result, our perspectives on the ethical and societal impact of BCIs are based primarily on gut reactions, either "the wisdom of repugnance" (as exemplified by Francis Fukuyama's nomination of transhumanism as "The World's Most Dangerous Idea, 2004") or the blind faith that technology can fix and improve everything (as exemplified by the mission statement of Humanity+, which promotes "the ethical use of technology to expand human capacities…[to make them] better than well" (http://humanityplus.org/).

In this essay, we describe an approach to the ethical analysis of BCIs that resists the emotional pull of futuristic scenarios without denying the importance of the questions they raise. In so doing, we address the more prosaic ethical issues that confront us now, which are too often overshadowed by the more sensational prospects of cyborgs, mind control and transhumanism. Finally, we indicate pathways through which seemingly fantastical futuristic scenarios can be more knowledgeably anticipated and addressed.

THREE ERAS OF BCIS AND THEIR ETHICAL CHALLENGES

As an organizing framework, we will distinguish among three different eras of BCI development, near-term, medium-term, and long-term, and distinguish among the different ethical issues associated with each.

LONG-TERM CHALLENGES

The futuristic ethical concerns already mentioned arise in the long-term future. We define this era as when BCIs are routinely used to augment human brains, giving users perceptual, cognitive and motoric abilities that may greatly exceed those of the unenhanced, and transforming emotional life as well. At this point, cyborgs will differ radically from unenhanced humans. One concern is that they will view us as a different, and inferior, life form, much as we now regard chimpanzees (Warwick, 2003). Loss of individuality is another long-term future scenario. If BCIs are used for direct brain-to-brain contact, this would enable new modes of communication but also lead to the possible replacement of individual mental lives by a network in which individual brains are mere nodes (Warwick, 2003).

Thoughts, feelings and memories that can be stored and shared as bits of data will not degrade as readily as human brain tissue. While other prosthetics such as artificial hips or heart valves can replace failing bodily structures, BCIs offer the first possibility of increased longevity of a person's consciousness. Immortality may even be possible (McGee and Maguire, 2007).

These BCI scenarios lead to interesting questions about what it means to be human. Would we be human if we could see infrared light, memorize a phone book, or cause others to move by willing them to with our own mind? Would we be human if we ceded the role of smartest beings on earth to others, or would those enhanced beings be humanity's new form? Would we be human if our minds never operated independently from others'? If they operated for eternity? These questions raise the more general question of what it means to be human, and also the question of whether being human by any particular definition has intrinsic value. Although these questions are age-old, they arise with a new urgency in connection with advanced BCIs (McGee and Maguire, 2007).

BCIs could eventually bring about tectonic societal shifts. The effects of cochlear implants on deaf culture (Tucker, 1998) may presage the impact of BCIs on all aspects of human culture that are adapted to current human capabilities rather than the augmented, networked capabilities of future cyborgs. Global political trends such as the Arab Spring, attributed in part to social networking, could be distant harbingers of the effect of wide bandwidth BCIs that enable the sharing of thoughts and feelings among groups of individuals.

MEDIUM-TERM CHALLENGES

The ethical challenges of the medium term will be largely free of the existential and metaphysical dimensions just discussed, such as ceding dominion of the earth to others, merging our identities into a global network, or questioning the meaning and value of being human. Yet the emergence of these medium-term challenges will depend on BCI technology advancing significantly beyond its current state and therefore do still have a science fiction flavor. We take the defining feature of the medium-term to be the availability of BCI therapies for a wide range of human afflictions.

One set of ethical issues at this point will concern barriers to delivery of BCI therapies. One barrier is likely to be economic. The cost of BCIs in the coming decades is hard to predict, as is future societal support for universal access, but we can anticipate some degree of inequity in access to BCIs. Patient acceptance of implants, in particular the bioethicists' "yuck factor" (Niemelä, 2011) may also prevent or slow delivery of BCI therapies.

Another issue with a degree of bioethical precedent concerns control of the BCI (Jebari and Hansson, 2013). Therapies vary in how much control patients have. How much adjustment or programming of a BCI by the patient will be feasible, and with what risks and benefits? An aspect of control with much less precedent concerns the possibility of BCI hacking, that is, the possibility that a third party, unbeknownst to patient and healthcare provider, would deliver inputs to a patient's brain or read brain states (Denning et al., 2009). Although safeguards against such interventions could of course be designed into any system, experience with current information technology shows that no system can ever be made entirely invulnerable to such attacks. This raises the dire prospect of hacking into systems controlling human thought, feeling and behavior.

Finally, as BCIs are adopted more widely for therapeutic use, enhancement uses will likely follow. The ethics of enhancement is a well-explored area in bioethics and neuroethics more specifically (Parens, 2000; Farah et al., 2014). However, compared to the effects of drugs, which only modulate function within existing brain networks, the addition of new sensory, action and computational devices has the potential to more radically enhance human capabilities.

The transition from therapy to enhancement is evident in many areas of medicine: from neuropsychiatry, where attention-boosting drugs are used by college students to enhance their focus and improve their grades (Sussman et al., 2006), to plastic surgery, where techniques developed to reconstruct injured faces are now commonly used to enhance the attractiveness of the uninjured. Therapeutic implantation of BCIs for only mildly impaired individuals could provide a bridge between therapy and enhancement uses of BCI. Another pathway along which BCIs could transition from therapy to enhancement is by the addition of enhancing BCIs for someone who is already undergoing therapeutic implantation for a serious disorder, for example increasing the range of wavelengths perceived by someone with impaired vision.

NEAR-TERM CHALLENGES

Compared with the challenges awaiting us in the medium and long-term, which are currently speculative, we are now faced with a set of ethical challenges that are clear and present. How we respond to these challenges will determine the path we take to the medium- and long-term challenges of BCIs. One set of ethical challenges concerns clinical trials—how trials are conducted and which indications are pursued. Economic considerations of course shape these decisions, and the ethical issue is how these considerations will be balanced by other considerations. Will BCIs be developed only for the most profitable applications, leaving numerous "orphan" medical conditions unaddressed? How will an emphasis on profitability shape the future of BCI technology, by advancing technology for certain applications over others?

A related set of immediate challenges concerns ownership of products during research and development. The finances of pharmaceutical research and development has been identified as an impediment to discovery and innovation (Cohen, 2005), as well as a disincentive for scientific objectivity and transparency (Goldacre, 2013). Given the extensive collaboration of academic and other publicly funded researchers with privately held device manufacturers, how should we design intellectual property agreements, clinical trials and regulation to maximize innovation and patient benefit?

APPROACHING THE FUTURE STEP BY STEP

We cannot help but approach the future step by step. In contrast, ethical analyses sometimes jump ahead. This is motivated by the commendable desire to anticipate, and therefore more effectively address, the ethical issues of the future. But this long-term ethical forecasting can be counterproductive. One reason is that it takes our attention away from the vitally important, if more mundane, ethical issues of today. Pondering what it means to be human may be more interesting than projecting research and development

Table 1 | Three eras of BCIs and their corresponding ethical challenges.

Time period	Characteristics	Ethical challenges
Long-term	Extensive enhancement of human brains with BCIs	Transhuman cyborgs' treatment of humans as inferior and inconsequential
		Vulnerability of those with BCIs to thought control and mind-reading
		Loss of individuality to a merged group mind
		Immortality of thoughts, memories and whole minds
Medium-term	Routine use of BCIs as therapy	Cost of BCIs as an obstacle for needy patients
		Discomfort or disgust with implants as an obstacle for patients
		Question of who controls operation of patients' BCIs
		Security of BCIs against hacking
		Acceptance of BCIs for enhancement of normal function
Near-term	Use of BCIs in a translational research setting	Conduct of clinical trials
		Developing BCI systems that maximize benefit as opposed to profit
		Ownership of intellectual property as an impediment or incentive to biomedical advances
		The influence of funding sources on research priorities

output under different intellectual property regimes. However, there is only one opportunity to get current decisions right, and that is now. Another reason is that bioethical decisions depend not only on values and principles, but also on the facts of the matter, which we have limited ability to anticipate in the distant future. Only as we live through each of the eras summarized in **Table 1** will we be positioned to predict the likely empirical constraints on the ethical decisions of the next era.

For example, how current BCI work is financed, who controls intellectual property and so forth, will set our course toward the next set of issues, the decisions on what gets commercially developed, how patients get access, and what kind of enhancements are available. Then, depending on our experience with whatever mix of technologies is developed in that medium-term period—which sensory, motor and cognitive systems can be effectively augmented for therapy and enhancement, what unanticipated benefits and harms emerge—we will have a much better platform from which to foresee and address the currently imponderable long-term ethical challenges of BCIs and transhumanism.

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Enhancement for well-being is still ethically challenging

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> *"If we were to ask the question: 'What is human life's chief concern?' one of the answers we should receive would be: 'It is happiness.' How to gain, how to keep, how to recover happiness is in fact for most men at all times the secret motive of all they do, and of all they are willing to endure." (William James, 1902).*

Enhancement is generally understood as being intended to improve well-being. The motivation to enhance is the desire to change a person for the better. However, even when increased well-being is the motivation, it is unclear how to morally evaluate any given intervention. Four examples illustrate why any enhancement intervention, including those motivated by the desire to increase well-being, still demands ethical reflection.

ENHANCEMENT—VAGUELY DEFINED AND CONTROVERSIAL

Humans have always been fighting, with all the means at their disposal, against disease, pain, and unhappiness, fighting to increase their quality of life. There have been many facts, fictions, and controversies around the enhancement of brain functions in the last 15 years. Ever since the debate started new definitions of enhancement have been proffered, often diverging from each other and leading to debates on a wide field of ethical and social matters (Parens, 1998; Farah et al., 2004; Levy, 2007; Greely et al., 2008; Schermer et al., 2009; Nagel, 2010b). Enhancement interventions come in many varieties: there are manifold methods, goals, motivations, desires, ideals, and values that can invoke heated discussions. Moral deliberation reaches from statements such as those put forward in the President's Council on Bioethics report Beyond Therapy (2003) with an anti-enhancement agenda mainly based on arguments around the concepts of naturalness and dignity, to arguments for the moral obligation to enhance (Harris, 2005; Savulescu, 2005)[1]. This wide variety in moral evaluations partly seems to be based on different understandings of the very term. Although "enhancement" is a notoriously vague term, a general consensus of what is meant is often implicitly assumed.

MOTIVATION AND GOAL: WELL-BEING

Here, I will attempt to further a particular understanding of the concept that shall serve to improve mutual understanding of the different positions. Furthermore, I suggest distinguishing what enhancement *is* and *how it is motivated* from how its usage is ethically evaluated. Julian Savulescu and colleagues distinguish various ways of conceptualizing enhancement and propose a "welfarist definition of human enhancement: Any change in the biology or psychology of a person which increases the chances of leading a good life in the relevant set of circumstances. (....) It singles out well-being as one dimension of value that is constitutive of genuine human enhancement." (Savulescu et al., 2011, 7). Brian Earp and colleagues contrast this welfarist approach with the "augmentative functionalist approach" to show how diminishment can be enhancement (Earp et al., 2014). John Harris elaborates on how enhancement is about making us better people: "Enhancements will be enhancements properly so-called if they make us better at doing some of the things we want to do, better at experiencing the world through all of our senses, better at assimilating and processing what we experience, better at remembering and understanding things, stronger, more competent, more of everything we want to be (. . .) In terms of human functioning, an enhancement is by definition an improvement on what went before. If it wasn't good for you, it wouldn't be enhancement." (Harris, 2007, 2ff). Enhancement is understood as generally being *for the better* of people. If it was not for an improvement for the better of an individual we would not call it enhancement. In fact, it is a tautology to say "enhancement for the better" as enhancement implies that it improves a given state, a performance, a capacity, an appearance, but also an experience, a feeling and, importantly: one's evaluations thereof.

EVEN WHEN IT IS FOR THE BETTER IT IS NOT ALWAYS GOOD: MOTIVATION DOES NOT EQUAL EVALUATION

A popular slogan about enhancement is that it makes people "better than well" (Elliott, 2003). Back in 1998, Erik Parens asked: "is better always good?" The problem actually is what "the better" really is in the plethora of possible cases of individuals in their unique socio-cultural contexts. How to evaluate what is better for a person, for his or her surrounding, or for the wider social context is a central matter for the normative discussion about it (Nagel, 2010b; Racine, 2010; Glannon, 2011). Hence, it is useful to inquire about the purpose of the particular enhancement intervention. Enhancements are usually not driven by the motivation to have merely *more* of

[1] Peter Reiner provides a lucid analysis of how this discussion is deeply bio-political, and driven by strong intuitions of those at the extremes (Reiner, 2013).

some capacity, but rather by the desire to change for the better[2]. Restricting the concept of enhancement to the addition of capacities or augmentation of function (Bostrom, 2009) does not do justice to the rich variety of forms which enhancement can take, and underestimates the plethora of motivations of people striving for enhancement. The goal of enhancement is improvement. One can argue whether one understands it as improvement beyond the normal, or improvement beyond the natural (Sabin and Daniels, 1994; Daniels, 2000; Buchanan, 2008, 2011)—both understandings lead to their own complex debates, and the concepts themselves require more scrutiny than this article can offer. Each view comes with its problems, and the consequent moral evaluations differ depending on what people feel most committed to (Parens, 2005). First and foremost, the goal of enhancement is about what people strive for most: "How to gain, how to keep, how to recover happiness" as William James put it in 1902. However, while interventions may indeed be motivated by the desire to increase flourishing, it is far from clear that the interventions indeed yield this increase in well-being. This view does not imply a normative evaluation of the enhancement intervention in a particular case. John Harris states that "enhancements *per se* are not ethically problematic: they are unequivocally good, clearly ethical. Unless the downside can be demonstrated and is significant, enhancement has the moral high ground" (Harris, 2005). While one might agree that enhancement *per se* always aims for something good, i.e., well-being, the evaluation of an enhancement varies between individuals depending on their situation. The moral evaluation of the intervention in specific cases does not depend solely on the desired goal of the intervention.

[2]I have argued elsewhere that "more" can even have negative effects on well-being (Nagel, 2010a). This refers not only to side effects and long-term effects but also to the potential burden of increased responsibility. Responding to this, John Danaher has argued that this objection does not justify the project to "forestall or delay the enhancement" project (Danaher, 2013). However, forestalling the enhancement project is not the goal of expressing this concern. The goal is to illustrate the need for closer scrutiny of the diverse influences of enhancement on well-being.

ETHICALLY CHALLENGING EVEN THOUGH WELL-BEING IS THE GOAL

The following examples should help clarify the general notion of enhancement as meaning "enhancement for the better," and demonstrate how this still leads to complex moral challenges.

1) **The usage of methylphenidate and amphetamine products in children for enhancement purposes, e.g., to improve cognitive functioning:** Despite the fact that data on side effects and effectiveness is sparse, usage of prescription medication for enhancement is increasing (McCabe et al., 2011; Smith and Farah, 2011; Kaye and Darke, 2012). For pediatric enhancement, one can assume that parents act with the best intentions for their children. They aim to foster their children's flourishing and often hope to do so with some form of enhancement. Thus, while striving for the best for their children and thus aiming at "enhancement for the better," they might still risk the child's current and future well-being (e.g., Urban and Gao, 2014). Over and above the individual impact, there are many pressing social issues surrounding pediatric neuroenhancement (Singh and Kelleher, 2010; Graf et al., 2013).
2) **Using neuro-technologies and psychopharmacology to induce plasticity for general-purpose enhancement:** Trans-cranial electrical stimulation like transcranial direct current stimulation and transcranial random noise stimulation can be employed as tools to induce neuroplastic cortical excitability alterations (Nitsche and Paulus, 2011; Cohen Kadosh, 2013; Snowball et al., 2013; for discussions see Cohen Kadosh et al., 2012; Fitz and Reiner, 2013; Davis and van Koningsbruggen, 2014; Krause and Cohen Kadosh, 2014). Furthermore, the commonly used anticonvulsant and mood stabilizer Valproat has recently been shown to induce plasticity, thereby reopening critical periods for learning (Gervain et al., 2013). These technologies seem to promise general enhancement potential by targeting neuronal plasticity. They certainly can be used for the better of the users. Crucially, however, this depends on the risk and side-effect profile. Moreover, ethical questions go beyond purely individual reasoning and must consider normative questions related to the values that a society wants to promote. This requires a cautious approach that can only be hinted at here. Paramount is the realization that "enhancement for the better" still offers challenges that require ethical reasoning.
3) **Using psychopharmacological agents to erase or modify memory:** Unpleasant memories diminish life quality. Especially individuals who have experienced trauma or shock can suffer from horrible, haunting memories. Manipulating such memories or their emotional intensity promises to increase well-being. While critics argue that for individual, social, and legal reasons "routinely interfering with the memories of trauma survivors and witnesses is highly questionable." (President's Council on Bioethics, chapter 5, IIC, Schacter, 2001), the motivation for even healthy people to seek memory blunting (e.g., with beta-blockers) is the desire to flourish. For the purpose of the present argument, the key aspect is this: Memory blunting as enhancement may help well-being but still requires ethical reasoning (Glannon, 2006; Kolber, 2006).
4) **Enhancing by amputation?:** A particularly challenging case for describing what enhancement could mean if one strongly stretches the concept into the realm of treatment, is an intervention in cases of Body Integrity Identity Disorder (BIID). BIID is a rare disorder in which patients suffer a complete lack of identification with a healthy limb and obsessively desire its amputation (First, 2005). They suffer sometimes so strongly that they will harm themselves to get rid of the unwanted limb. In these cases, amputation reduces anxiety, relieves suffering, and increases the amputees' subjective quality of life. Despite the unclear medical categorization, and despite the fact that these patients suffer from a disorder, and thus interventions qualify as treatment rather than enhancement, the dilemma

is strong: There are patients with BIID who can decide autonomously for elective amputation that harms their physical body but enhances their well-being (Bayne and Levy, 2005). Approaching such an amputation as enhancement is provocative, shatters intuitions, and thereby demands clarification of what is meant by enhancement.

HOW TO PROCEED?

Various situations of enhancement can lead to more flourishing. However, this does not foreclose ethical discussions. Ethical dilemmas emerge even if the goal of the intervention is increased well-being. I agree with Erik Parens who notes that "some (…) think the term enhancement is so freighted with erroneous assumptions and so ripe for abuse that we ought not even to use it. My sense is that if we didn't use enhancement, we would end up with another term with similar problems" (Parens, 1998, 2). Clearly, there is still work to be done to clarify what we mean with enhancement. Future deliberation should include two issues that have not yet been considered sufficiently in current debates: (1) Studying the nature of well-being, and how it can be increased (Parfit, 1984; Kagan, 1992; Nussbaum and Sen, 1993; Scanlon, 1998), and (2) probing public attitudes on enhancement to allow regulation and political decision-making to be nuanced and sound (Nadler and Reiner, 2010; Fitz et al., 2013). While working on this, it is worthwhile to avoid clamoring for a binary position either "for" or "against" enhancement in general, and instead foster sensitive discussions about the concerns and idiosyncrasies of each different case.

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The ethical, moral, and pragmatic rationale for brain augmentation

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This opinion paper discusses the importance of augmentation in general and brain augmentation in particular, and considers the merits of some arguments that have been made against it. Augmentations are technologies created in order to improve upon human capabilities and characteristics. Such technologies have had a profound effect on our species, and their omnipresence might be said to distinguish us apart from every other species more-so than anything aside from our DNA. Augmentations are so essential to us, so widespread, that we often forget that they are artificial, and not truly a part of us. Indeed, if all augmentations were lost to us and could not be replaced, without any viable means to feed and protect ourselves, most humans would be dead in very a short time.

The need for augmentation is related in part to our poor biological adaptations for survival. We are born without claws, fur, and other characteristics that most animals require. What evolution has endowed us with instead is a large and complex nervous system. Our brains are metabolically expensive, requiring over 20% of our metabolism, while representing only 2% of our body mass (Kety, 1957; Sokoloff, 1960; Rolfe and Brown, 1997). Large brains are also difficult to grow, causing potential problems in childbirth as the baby's head must pass through the birth canal, and a long childhood is required to learn the minimum needed for survival and to become a member of society. However, they provide us with the means to compensate for our physical limitations. We can imagine, create, and manufacture a variety of augmentations. Housing and clothing for protection, agriculture for food, transportation, medicine, and many others. Such physical augmentations have provided us with a means to expand our livable environment to include most of the planet, including underwater and outer space, and they satisfy our biological and emotional needs far beyond what would otherwise be possible.

Augmentative technologies include not only physical but also cognitive enhancements. Similar to physical enhancements, cognitive enhancements provide us with capabilities beyond that provided by our nervous systems, to maintain or expand our perceptual, cognitive, and affective capabilities. This includes such devices as telescopes, microscopes, hearing aids, television, the internet, and myriad other devices that expand our senses and allow us to perceive much more than our immediate environment. Cognitive enhancements also include writing and mathematics, which have provided tremendous benefits, matched only by the potential of the computer age, which has transformed our world in just a few decades, and is likely to continue to do so.

Learning how to use any augmentation leads to adaptive changes in the nervous system as new memories are encoded and procedures are automated. By contrast, neuroenhancement changes the nervous system directly, augmenting cognition, and behavior from the inside out. Current forms of neuroenhancement include psychoactive substances, biofeedback, cognitive training, methods that promote physical health such as nutrition and exercise, mindfulness, electromagnetic methods of neurostimulation such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) and others reviewed in Clark and Parasuraman (2014), and methods using ultrasound or near-infrared light. Indeed, neuroenhancement is not just "one thing" any more then exercise or learning is one thing, but instead covers a large and expanding array of different technologies.

Recent work in neuroenhancement has produced some surprising results. Work in our laboratory has shown that tDCS, a relatively simple technique that uses a 9-volt battery to produce a 1–2 mA current, led to large improvements in learning of a difficult visual perceptual task. Performance and d' (a measure of signal discriminability) were found to double while the false alarm rate was halved (Clark et al., 2012; Coffman et al., 2012b). This showed a dose-response effect (Clark et al., 2012), lasted for over 24 h (Falcone et al., 2012), and was not related to stimulation artifact or the type of experimental blinding used (Coffman et al., 2012b). TDCS also alters neurochemistry (Clark et al., 2011) and increases some forms of attention (Coffman et al., 2012a), which together and along with other effects may result

in these large improvements in behavior. Other laboratories have found that tDCS can be used to increase working memory, explicit and implicit memory, perception and attention (reviewed in Coffman et al., 2014), with an average increase in effect size of about 0.9 between active and sham across studies. Using different methods of stimulation, these forms of cognition can also be reduced.

It should be clear to the reader by now that augmentation is essential to human existence, that physical-, cognitive-, and neuro-enhancement are all important to us, and that continued development of neuroenhancement technologies may lead to even more useful forms of brain augmentation. While there is some debate about its ultimate utility (Walsh, 2013), most evidence suggests that with further development, these many forms of neuroenhancement will likely lead to at least a few useful applications, and perhaps many. However, recent advances in neuroenhancement have also led to claims that some types are too unusual, immoral or unethical and should be banned or heavily managed. These arguments take a number of different forms. I will next discuss a subset of these.

(1) Cognitive augmentations may provide benefits only to those few who can afford them, thus further widening the social and cultural gap created by income differences (discussed in Hyman, 2011).

Different technologies for cognitive augmentation vary greatly in their relative cost. DBS can indeed be very costly, requiring neurosurgery to implant a carefully manufactured devise. However, other methods such as tDCS are relatively inexpensive, using technology that is already widely available for other purposes, electrodes made of inexpensive materials, and a single 9-volt battery that can operate the device for hours. So, while some methods of neuroenhancement may be too expensive for many people, other methods exist that are more affordable. I suggest here that simpler, cheaper and safer methods of neuroenhancement, and indeed all medical technologies, should be developed and attempted for treatment first, and only when these are proven to be inadequate should more expensive and potentially dangerous methods be attempted. This would lead to the most cost effective, safe, and beneficial treatments becoming more widely available, while reducing the potential harm of treatment side-effects.

(2) Cognitive augmentation might lead to an enhancement "arms race," where all people are required to use enhancement in order to stay competitive (summarized in Hyman, 2011).

This concern may have some basis in fact. If we look at other forms of augmentation, those that are most useful are often adapted by the majority of people, to the detriment of those few who do not or cannot. Literacy provides an excellent example of this. Historically, literacy was limited to just a few, helping to maintain the sociopolitical structure, with those on top using literacy to maintain control. Once literacy was more widely disseminated, it helped to promote democracy and social change. Today, those who are illiterate are often relegated to lower-paying jobs, welfare, or crime to survive. Indeed, since literacy is so beneficial, it is most often caused by poor circumstances, rather than a personal choice. Might it be argued the literacy is unfair because it relegates most involuntary illiterates to the lowest levels of society, and therefore should be denied to all? If a form of brain-augmentation turned out to be as beneficial as literacy, would it be equally unreasonable to deny it to all in order to respect the choices of a few? I argue here that, as with literacy, mathematics, computer proficiency, and many other examples, an entire society should not be put at a disadvantage to appease those few who cannot or choose not to use an augmentation. Should there be additional costs in terms of safety or other issues, this becomes more complicated, and needs to be dealt with by weighing factual evidence carefully in terms of costs vs. benefits, and our commonly accepted sense of ethics. In order to do this adequately, published studies of neuroenhancement must use carefully controlled and replicable methods, provide statistics, and openly describeside effects and failures so that both costs and benefits can be well understood.

(3) Enhancements in one cognitive domain may lead to reductions in other domains (Brem et al., 2014).

This argument assumes that emphasizing one form of cognition must necessarily reduce others to maintain the total amount of cognitive function. While there is some evidence that decrements in one form of cognition can lead to enhancements in others (Luber and Lisanby, 2014), this hypothesis leads to a number of questions. For instance, is enhancement necessarily an increase in a specific cognitive "volume," or instead might other mechanisms be involved, such as reducing neural "noise," leading to increased neural SNR but without adding to cognitive load? Also, is total cognition stagnant, or does it vary over time? There is substantial evidence that it does, such as from birth to adulthood, and depending on state factors such as alertness, amount of sleep, nutrition, exercise, training and so on, and so enhancements that affect these may increase cognitive "volume" without reductions in other areas. Finally, if reductions are indeed found in other cognitive domains, the question arises of how important those domains are relative to those that are enhanced. In all cases, it's important to obtain reliable empirical data, and perform cost-benefit analyses before making firm decisions on whether cognitive- and brain-augmentations should be used.

(4) Uncertainty regarding safety is also an issue.

Potential dangers are present for all forms of brain augmentation, but the questions that should be asked are, "Is it as safe or safer than other methods currently in use?" and "Do the benefits outweigh the costs?" For some forms of neuroenhancement, their use might possibly cause harm. As an example, DBS produces damage during implantation, and can lead to bleeding, infection, and other issues that have resulted in the deaths of some patients (Rocha et al., 2014). However, most methods of neuroenhancement are unlikely to cause physical harm if used correctly. The use of any

medical augmentation should be based on published clinical trials when available, using methods approved by IRBs or other governing bodies. There are some important differences between pharmaceuticals and tDCS that suggest tDCS should be safer. TDCS can be ended in a few seconds, compared with a "wash out" period of days or weeks for some pharmaceuticals. TDCS can be directed to specific points on the head, while avoiding other organs such as liver, heart and kidneys, where deleterious side effects of pharmaceuticals can sometimes occur. Also the chance of forming unexpected chemical side products from interactions with other concurrent treatments is reduced. Overall, tDCS has far fewer and less dangerous side effects, limited to redness/irritation under the electrodes, mild tingling, itching, heat and less commonly fatigue, transient headaches, nausea, and insomnia (Poreisz et al., 2007). Furthermore, brain stimulation for pain treatment is much less likely to lead to addiction when compared with opiates. Based on these qualities, tDCS appears safer than pharmaceuticals for most applications. Once effective methods of brain stimulation for clinical treatment are developed in smaller studies, large scale clinical trials need to be performed in order to better understand their costs and benefits relative to the current standard of care. As an example, TDCS shows great potential for the treatment of a variety of illnesses, but few large-scale clinical trials have been performed thus far.

(5) A broader argument involves the potential risks imposed by our increasing dependence on modern technologies that might have unforeseen negative effects, resulting in our ultimate demise (Rees, 2003).

While the combined side effects of our technological world, such as pollution, population expansion, diminishing resources, and continued warfare may end our domination of Earth as soon as it began, at present we are at our peak in many ways. The possibility that an otherwise safe augmentative technology might lead to our demise is impossible to predict. We cannot see into the future, but we can look for patterns that may help us to estimate the likelihood of future events. Some technologies, such as landmines and nuclear weapons, can be argued to produce much more harm than good and should be banned. However, nearly anything can be used with the intention of doing harm. From sharpened rocks to rockets, from ancient writing to modern computers, even the wheel, nearly all technologies have been used to support warfare or to cause harm in some way. By contrast, cognitive- and brain-augmentation technologies have provided many benefits to us thus far, and will likely continue to do so. Our success has a species has primarily been derived through our intelligence and cognitive capabilities. Enhancing these further through the benefits of cognitive- and brain-augmentation, we might one day develop better, safer and more sustainable technologies to reduce pollution, better manage resources, reduce the need for or find alternatives to warfare, and improve our chances of survival overall, rather than reducing them.

SUMMARY

We can say with certainty that our species would be unlikely to exist as it does today without augmentation. Cognitive- and neuroenhancements are just the latest in a long line of augmentations that have helped our species to survive and flourish. While there are some valid concerns, the benefits of brain augmentations like tDCS will likely far outweigh their costs when properly used. The continued pursuit of cognitive- and neuro-enhancement will help us to improve our quality of life, reduce suffering from brain and mental illness, and enhance our chances of survival long-term.

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Pharmacological cognitive enhancement—how neuroscientific research could advance ethical debate

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There are numerous ways people can improve their cognitive capacities: good nutrition and regular exercise can produce long-term improvements across many cognitive domains, whilst commonplace stimulants such as coffee temporarily boost levels of alertness and concentration. Effects like these have been well-documented in the medical literature and they raise few (if any) ethical issues. More recently, however, clinical research has shown that the off-label use of some pharmaceuticals can, under certain conditions, have modest cognition-improving effects. Substances such as methylphenidate and modafinil can improve capacities such as working memory and concentration in some healthy individuals. Unlike their more mundane predecessors, these methods of "cognitive enhancement" are thought to raise a multitude of ethical issues. This paper presents the six principal ethical issues raised in relation to pharmacological cognitive enhancers (PCEs)—issues such as whether: (1) the medical safety-profile of PCEs justifies restricting or permitting their elective or required use; (2) the enhanced mind can be an "authentic" mind; (3) individuals might be coerced into using PCEs; (4), there is a meaningful distinction to be made between the treatment vs. enhancement effect of the same PCE; (5) unequal access to PCEs would have implications for distributive justice; and (6) PCE use constitutes cheating in competitive contexts. In reviewing the six principal issues, the paper discusses how neuroscientific research might help advance the ethical debate. In particular, the paper presents new arguments about the contribution neuroscience could make to debates about justice, fairness, and cheating, ultimately concluding that neuroscientific research into "personalized enhancement" will be essential if policy is to be truly informed and ethical. We propose an "ethical agenda" for neuroscientific research into PCEs.

Keywords: cognitive enhancement, brain function augmentation, ethics, modafinil, ritalin, justice, cheating, personalized enhancement

INTRODUCTION

Recent research in neuroscience and pharmacology has demonstrated that various pharmaceuticals can have modest cognition-enhancing effects in healthy individuals (for reviews, see Repantis et al., 2010; Husain and Mehta, 2011). For example, some studies have shown that modafinil—originally developed for the treatment of narcolepsy—can improve various dimensions of cognitive function in sleep-deprived (Wesensten et al., 2005; Thomas and Kwong, 2006) and non-sleep-deprived healthy adults (Turner et al., 2003; Müller et al., 2004). Similarly, methylphenidate—originally developed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)—has been shown to improve spatial working memory and planning in healthy adults (Elliott et al., 1997; Mehta et al., 2000).

Unlike the more mundane methods for improving cognitive function—such as exercise and good nutrition (Dresler et al., 2012)—these pharmaceutical cognitive enhancers (PCEs) are thought to raise a host of ethical issues for individuals and society (Greely et al., 2008; Bostrom and Sandberg, 2009). At the individual level, concerns are raised about medical safety and side effects, the authenticity of the enhanced mind and the value of achievements facilitated by pharmaceutical intervention. At the societal level, ethical questions can be asked about whether the availability of PCEs would increase or undermine equality, and about whether individuals will be directly or indirectly coerced into using PCEs. Further normative questions emerge particularly in the healthcare setting: should we be drawing a sharp line between treatment and enhancement and should individuals be given access to PCEs through medical professionals?

In this paper, we outline the key issues at stake in the normative debate about pharmacological cognitive enhancement (PCE) and, for each issue, suggest the contribution that neuroscientific research could make. The greatest contribution will be made to the discussions surrounding the safety and efficacy of PCEs. Although the question of what harms are worth risking in the pursuit of certain benefits is to a large extent normative, the dearth of evidence about the effectiveness and safety of PCEs in real-world contexts renders the discussion mostly hypothetical at this

point. More research on the risks of dependency is also urgently needed. Data of this kind will be crucial for discussions about regulation, and for debates about the permissibility of requiring or encouraging people to use PCEs.

In addition to the contribution neuroscience will make to understanding the risk-benefit profiles of PCEs, we suggest that a more nuanced understanding of the neural systems affected by different substances will enrich the debate about whether PCE use constitutes cheating. Also related to cheating, we further suggest that the neuroscientific evidence on the functional trade-offs precipitated by some PCE adds an important dimension to the debate about whether achievements facilitated by PCEs should be seen to be effortless and involve little sacrifice. Drawing together our conclusions, we propose an "ethical agenda" for future neuroscientific research on PCE. This agenda sets out what sort of research would help move the ethical debates forward, and why. Resolving these debates will be crucial for ensuring that society responds to the increasing use of PCE in the most responsible, fair and rational way. For a summary of our "ethical agenda" for neuroscientific research, see **Table 1**.

OVERVIEW OF PHARMACOLOGICAL COGNITIVE ENHANCEMENT

What it means to "enhance" is notoriously difficult to pin down. To enhance is essentially to improve or increase, but what this improvement must be relative to is not obvious. On the broadest definitions of enhancement, some capacity is enhanced if it is improved relative to its prior level of functioning such that it increases the individual's chances of leading a good life—enhancement thus occurs regardless of how well- or poorly-functioning the capacity originally was (Savulescu et al., 2011). On more restrictive definitions of enhancement, a capacity is enhanced if it is improved beyond a particular point—perhaps a species mean or agreed "normal" level of functioning (c.f. Sabin and Daniels, 1994). Others define enhancement as any improvement which goes beyond correcting pathology. For example: "A

Table 1 | Summary of ethical agenda for neuroscientific research.

Suggested type of study	Advancement in ethical debate
Longitudinal studies investigating the long-term safety profile of PCEs	This is perhaps the most pressing task for neuroscientists. The long-term, real-world safety profile of PCEs is of considerable import to potential users and to all debates about PCE ethics and policy. In relation to the latter concerns, longitudinal studies will advance ethical debates about: (1) whether PCEs should be placed on the open market for enhancement purposes (and with what restrictions), and (2) whether employees doing particular types of jobs can legitimately be required to take PCEs
Identification of pathology associated with mental or psychiatric disorders or limitations to enable classificatory separation of conditions which are diseases from those which constitute normal human variation	Will advance the ethical debate about whether the administration and effects of particular PCEs constitute treatment or enhancement, and how resources should be deployed accordingly
Identification of the effects of PCEs in targeted and specified populations of ethical significance, such as those who are worst off. In particular, further research into the baseline effect should be conducted	Will advance the debate about distributive justice and access to PCEs. If PCEs have differential effects on those who are already worst off, this will be highly relevant to their permissibility and just distribution
More precise distinction between the different cognitive effects of different PCEs	Will (1) be of central relevance to whether certain putative PCEs will be used for enhancement and, if so, in which contexts and (2) advance the debate on cheating in competitive contexts: some effects (e.g., creativity) might be considered more unfair than others (e.g., wakefulness) and enhancing motivation vs. enhancing effectiveness might be considered relevant to the value of any resulting achievements
Investigation of the functional trade-offs associated with different PCEs	Will (1) be of central relevance to whether certain putative PCEs will be used for enhancement and, if so, in which contexts and will (2) advance the debate about the nature of the sacrifice possibly required for achievements to have value. It will also (3) advance the debate about the practicality and legitimacy of requiring certain people to take PCEs
Pursuit of a "personalized enhancement" approach to bring us closer to understanding what effect any particular PCE will have in any particular person	Will be relevant to many (if not all) ethical debates and policy considerations including: (1) whether particular people could legitimately be required to take PCEs in certain contexts, (2) who should be given priority access to which PCEs, (3) whether unequal effects have ramifications for cheating. Only when we can predict the *personal* benefits and costs of enhancement can policy be truly informed and ethical

cognitively enhanced person [. . .] is not necessarily somebody with particularly high (let alone super-human) cognitive capacities. A cognitively enhanced person, rather, is somebody who has benefited from an intervention that improves the performance of some cognitive subsystem without correcting some specific, identifiable pathology or dysfunction of that subsystem" (Bostrom and Sandberg, 2009). In this paper, we adopt the broader understanding of cognitive enhancement. We do this in part because the substances currently available and likely to be available in the near future effect only modest improvements (Husain and Mehta, 2011), but also because we believe that any line intended to mark the point at which an improvement counts as enhancement necessarily involves a value judgement involving normative (ethical) considerations.

Most of the substances cited as putative PCEs were originally developed for clinical use, to treat conditions that are at least partly characterized by some observable cognitive defect. Here, again, it is sometimes difficult to decide what should count as a cognitive *defect*. However, in the case of defective or deficient capacities, decisions must be made about where to place the line to determine who should receive medical attention and resources. For example, two of the substances receiving the most attention from those interested in enhancement—methylphenidate and modafinil—were originally developed to treat the symptoms of ADHD and narcolepsy, respectively. More recently, however, these substances have been used off-label by healthy individuals to improve their memories, level of alertness, or powers of concentration (e.g., Maher, 2008). Other substances with some modest enhancing effects on cognition include donepezil, dopamine agonists (such as d-amphetamine, bromocriptine, and pergolide), guanfacine, atomoxetine, reboxetine, galantamine, rivastigmine, and memantine. Working pharmacologically in different ways, these substances have been shown to improve cognitive functions such as response inhibition, working memory, episodic memory, attention, vigilance, and incidental learning (see de Jongh et al., 2008; Lanni et al., 2008; Husain and Mehta, 2011). However, this limited evidence of effectiveness should be cautiously considered alongside studies producing null results and some evidence of task-specific impairments (see Hall and Lucke, 2010 and Advokat, 2010 for less optimistic reviews of the scientific literature on PCE).

The prospect of being able to enhance any of these cognitive functions probably would be attractive to many individuals. Whether the goal of such enhancement would be to perform better at work, to learn a skill or language quicker, to decrease the need for rest in leisure time, or even just to experience one's mind as "sharper," improving cognition would presumably come with many benefits. Data from various prevalence studies indicate that there are groups of individuals who use some of the substances listed above for purposes of studying, to combat jet-lag or even to facilitate completion of household chores (for a review of student uses, see Smith and Farah, 2011; see also Maher, 2008).

Whilst the neuroscientific literature is reporting some modest enhancement effects of these substances on the cognition of healthy individuals (c.f. Husain and Mehta, 2011), the ethical literature has been raising and responding to a variety of issues pertaining to their use (for overview see Greely et al., 2008; Bostrom and Sandberg, 2009). Some of these issues are practical, some socio-political and others relate to the individual user. The overarching goal is to ascertain how permissible and how moral PCE use is and how society and regulatory bodies should respond to it. Although the ethical debate is principally a normative enterprise, it cannot reach firm conclusions about how to proceed based purely on hypothetical reasoning and untutored speculation: it must be informed by neuroscientific research providing the empirical facts about PCEs. In what follows, we outline the key issues in the enhancement debate, emphasizing where we think neuroscientific research might have particular importance for the normative debate.

ETHICAL DEBATE AND THE RELEVANCE OF NEUROSCIENTIFIC RESEARCH

MEDICAL SAFETY AND EFFECTIVENESS

In many ethical discussions of cognitive enhancers the first issue to be raised (often to be set aside so that there can be any further discussion at all) is whether cognitive enhancers are *medically safe* to use. Since there are no longitudinal studies yet examining the long-term use of pharmaceuticals such as modafinil and methylphenidate, some authors argue that we currently do not know enough about the potential dangers and that the availability and use of PCEs should be avoided on this basis (e.g., Drabiak-Syed, 2011; Boot et al., 2012).

Despite the huge interest in PCE from philosophers and scientists, the evidence of their *effectiveness* is still inconclusive. Moreover, where there is evidence of enhancement effects, they often tend to be limited to improvements on specific tasks, are only seen at certain dosages and are not observed in all people (Ragan et al., 2013; Farah et al., 2014). Crucially, it must be remembered that the degree and nature of any cognitive improvements will be different for each PCE and so no sweeping claims should be made about the effectiveness of PCEs in general. In terms of both effectiveness and safety, it should also be noted that short term studies carried out in laboratory settings are not representative of long term use in real world contexts.

In his meta-analysis of randomized controlled trials of methyphendidate, Repantis et al. (2010) found a significant improvement in the long-term memory of healthy participants, particularly when there was a longer interval between the learning phase and recall. However, the meta-analysis revealed no significant improvements in attention, mood or executive functions. Similar findings emerged from Farah et al.'s (2014) review of more than fifty experiments on the effects of amphetamine and methylphenidate: they found convincing evidence of an enhancing effect of stimulants on learning under some circumstances, specifically when the retention interval between study and test was longer than an hour, but not at shorter intervals. They also concluded that the evidence for improvement of executive functions was much less clear. There is some evidence to suggest that the effects of methylphenidate on cognitive control are only significantly positive in participants whose performance on placebo was lowest (Smith and Farah, 2011).

In relation to the effectiveness of modafinil, Farah et al.'s (2014) recent review of single dose studies of modafinil concluded that there is clear evidence of enhanced executive function

and memory for sleep-deprived individuals but, for rested adults, whilst there were some positive findings for specific tasks such as those requiring inhibitory control, there were also a large number of null results and the occasional finding of impairment. They refer to this pattern—of limited improvements on some specific tasks and impairment on others—as being "familiar" for PCEs.

There are also some reviews of the effectiveness of anti-dementia medications for cognitive enhancement. These include acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine. A review conducted by Repantis (2013) concluded that the few existing studies of effects in healthy participants provide no consistent evidence for a neuroenhancement effect. In the case of, donepezil there was some evidence to suggest improvements on retention of training on complex aviation tasks (Yesavage et al., 2002), improvements in verbal memory and episodic memory (Gron et al., 2005). However, other studies showed no or limited effects on memory and attention and two others showed transient impairment of episodic memory (Beglinger et al., 2004, 2005). The same pattern of results suggesting enhancement in some cases but no effect or even impairment in others can be seen for donepezil. Further, a review of the efficacy of these putative cognitive enhancers for patients with mild cognitive impairment concluded that they did not improve cognition or function among patients with low-level impairment (Tricco et al., 2013).

The *medical safety* of PCEs varies from substance to substance, and side effects relate not only to the direct pharmacological effects but also to broader psychological and physiological changes. The review conducted by Repantis (2013) concluded that in the majority of trials, the drugs were well tolerated. However, side effects were noted. In relation to methylphenidate, side effects included increased heart rate and some instances of increases in blood pressure. Headaches, anxiety, nervousness, dizziness, drowsiness, and insomnia were also typical complaints.

Repantis (2013) summarizes similar side effects for modafinil, where adverse reactions included headache, dizziness, gastrointestinal complaints (e.g., nausea, abdominal pain, dry mouth), increased diuresis, palpitations, nervousness, restlessness, and sleep disturbances and insomnia (especially in studies with non-sleep deprived individuals). In their recent review, Ragan et al. (2013) highlight the fact that modafinil was reviewed by the European Medicines Agency (2010), who concluded that it should not be prescribed for obstructive sleep apnea, shift-work sleep disorder, and idiopathic hypersomnia because of the risks of serious skin reaction, suicidality, depression, psychosis, and adverse cardiovascular events.

In relation to anti-dementia drugs, Repantis (2013) concluded that, in the majority of the trials in healthy adults, donepezil was well tolerated. However, some side effects were reported in some participants, including gastrointestinal complaints (e.g., nausea), headaches, dizziness, nightmares, and insomnia. The meta analysis of anti-dementia drugs for people with mild cognitive impairment (Tricco et al., 2013) revealed that patients taking these medications experienced significantly more nausea, diarrhea, vomiting, and headaches than patients taking placebo. The authors also suggest that patients taking these medications might be at greater cardiac risk, with one study finding a higher incidence of bradycardia among patients who received galantamine.

As Farah et al. (2014) emphasize, there is another type of risk that should not be ignored in a consideration of the safety of PCEs. Many pharmaceuticals, especially stimulants, present a risk of dependence. The authors cite a nationwide survey analyzed by Kroutil et al. (2006) which estimates that almost one in twenty nonmedical users of prescription stimulants meet the criteria for dependence or abuse (For further discussion of the potential for addiction in student populations see Outram, 2010 and White et al., 2006).

Finally, as Ragan et al. (2013) point out, there is no such thing as a completely safe drug, only a drug whose benefits outweigh its drawbacks. However, it is also worth emphasizing that, even if there are long-term risks associated with these substances, this does not (by itself) mean that they should automatically be prohibited. There are serious risks associated with many activities that the state permits because it is believed that individuals should decide for themselves whether these risks are worth taking. Dangerous sports and cosmetic surgery both come with risks, but the value some individuals attach to the respective sporting experiences and cosmetic effects justifies giving these individuals the choice to take risks in their pursuit.

This caveat notwithstanding, and taking into account potential costs to the healthcare system, greater knowledge about safety and efficacy will allow regulators to decide whether the decision about which risks are worth taking should be put in the hands of consumers (for a detailed discussion of the way risks and benefits should be assessed for cognitive enhancement devices, such as brain stimulators, see Maslen et al., 2014). The ethical debate about the level of risk consumers should be allowed to take is of great practical importance when it comes to making policy recommendations. In addition, the question of whether the harms of a certain PCE outweigh its benefits will be important to discussions about the permissibility of requiring individuals to use PCEs and about the possible need to protect individuals from pressure to take any of the substances under discussion.

Finally, the empirical project of identifying the different effects PCEs have across a different individuals (c.f. Husain and Mehta, 2011) is likely to feed into the normative debate about which effects (for which individuals) constitute a form of treatment and which effects (for which individuals) constitute enhancement. We discuss these and other ethical issues in what follows.

AUTHENTICITY AND NATURALNESS

There are a bundle of related ethical issues that are sometimes raised under the broad heading of *authenticity* (see Bublitz and Merkel, 2009; Juth, 2011). Some of these pertain to numerical personal identity—do individuals become categorically different persons when they transform themselves via enhancement? (DeGrazia, 2005)—some consider less drastically what it is for an individual to be to be more or less his or her "real" self (The President's Council on Bioethics, 2003), and other ethical concerns pertain to what it is to be, and function as, a human being (Kass, 2003).

The principal tenet underlying authenticity objections against the use of PCEs is that individuals are most themselves when they are in their "natural," unaltered state. If capacities and characteristics fundamental to one's identity are changed, then the individual is recast as an altered or inauthentic person (e.g., Elliott, 1999). This argument is premised on the idea that there is a "real," true self, and that this real self is to be preserved as much as possible. However, this assumption can be challenged: individuals often (and understandably) try to improve themselves in ways that allow them to more successfully achieve their goals. Being autonomous is to form goals for how one's life is to go, including what kind of person to be. On this model of authenticity as autonomy, whether PCE is authentic depends on whether it helps a person to achieve her autonomous goals. For example, an individual might teach him or herself motivational strategies to overcome his or her naturally lazy disposition; another individual might use techniques from cognitive behavior therapy to overcome his or her propensity for generalized anxiety (e.g., Butler et al., 2006) or shyness, or gregariousness, or bad temper, or gullibility. Such strategies may not render the individuals inauthentic, but rather assist them in removing barriers that otherwise prevent them from maximizing self-actualization. Correspondingly, if PCEs can, for example, help an individual to concentrate better so that he or she can achieve the goals he or she values, this acts in service of authenticity rather than undermines it. There is great human variation, and variation within individuals subject to many intrinsic and extrinsic factors (see Kahane and Savulescu, 2013). Even if the authentic self were defined, it seems likely that many factors interfere and PCEs may reduce the effect of such influences.

However, some deny that authenticity is reducible to autonomy. Such writers (e.g., Taylor, 1991) appeal to a "real self." But even on such an account, the real self may be complex and multifaceted. Often people have a range of qualities and they may use PCEs to bring out some of their qualities, while suppressing others. Thus, whether an enhanced self compromises the real self depends on what constitutes a person's real self and what the effect of the PCE is—both questions for cognitive science. If PCEs merely amplify, rather than add entirely new qualities, then they enable the self to evolve, rather than replacing one individual with a set of attributes with another with different attributes.

There is a related but different concern about *naturalness*. The idea that enhancements will take us too far from what it is to be human altogether is often accompanied by the idea that too much technological intervention will lead to an overmechanization of the mind. The activities in which we engage—and, more importantly, the ways in which we engage in them—are said to have a certain quality to them that makes them "human" activities (President's Council on Bioethics, 2003). In this vein, Kass (2003) argues that since individuals play no role in bringing about the effects of biomedical interventions, they cannot understand these effects "in human terms." His suggestion is that whereas the effects of studying or training are "intelligible" to us, the effects of direct interventions are not comprehensible and thus our use of them departs "from "genuine," unmediated, and (in principle) self-transparent human activity" (p. 23).

However, we argue that we make use of many directly-acting substances, in medicine and in leisure, that do not result in departure from "genuine" human activity. Just because their pharmacological mechanisms are not understood by the average person does not mean that they cannot be made sense of as part of a human narrative. Kass cites alcohol, caffeine and nicotine as not having the same unintelligible quality as direct biomedical interventions. He says this is because "we use these agents not as pure chemicals but in forms and social contexts that, arguably, give them a meaning different from what they would have were we to take them as pills" (p. 22). An obvious objection to Kass' resistance to PCEs would be to add PCEs to beverages, as caffeine currently is. It would then be "intelligible" in the same way that caffeine is said to be "intelligible." Moreover, if intelligibility can be conferred by social context then the social context of, for example, studying, or conducting research should equally make PCEs part of a comprehensible human enterprise. Perhaps his distinction between the forms alcohol, caffeine, and nicotine tend to take, and the form of a simple pill, is supposed to indicate that the former are enjoyed for themselves, rather than being instrumental to achieve some goal. However, studies have reported that some individuals take PCEs for recreational purposes (see Smith and Farah, 2011) and it is common knowledge that caffeine is regularly used exclusively for alertness and for performance enhancement. Even if it might be the case in lay people's current perceptions (cf. Faulmüller et al., 2013; Schelle et al., 2014), from a normative stance it cannot be that form and context make all the difference between the human intelligibility of an espresso and a caffeine pill and a PCE.

The core of such an "intelligibility" objection may be that PCEs and other new technologies work in ways entirely alien to the way the human mind normally works, adding a completely new way of being. For example, chips inserted into the human brain that allowed us to perceive other people's thoughts directly would be entirely new. Neuroscience can assist by unravelling the way the mind does work, and does not, and by enabling categorization of enhancers into those which harness natural processes, and those that introduce entirely new capacities. Most enhancers at present appear to harness existing neurobiological physiology, though exactly how many enhance performance remains to be determined.

The ethical debate about authenticity and naturalness is unlikely to be advanced solely by the findings of neuroscientific research. The disagreement is partly a normative one about what constitutes the "real" self and whether our "real" selves are the selves we are most prone to being or the selves that we aspire to develop in to—or whether it makes sense to speak of "real" selves at all. Qualitative research, such as that conducted by Singh (2005) or Bolt and Schermer (2009), will helpfully provide a clearer picture of the sorts of experiences individuals have when taking PCEs.

In summary, it is important to recognize that most PCEs, if not all, harness innate biological systems, for example, affecting release, reuptake or sensitivity to neurotransmitters that cause cognitive activity. They do not at present introduce radical "new ways of being" divorced from the ordinary human way—they really just provide "more of the same." Indeed, humans vary in

the ways in which their cognitive systems function and in some cases, PCEs may bring those at the lower end of normal up to the level of function of those in the mid to upper range.

More importantly, we suggest that what matters more than whether the experiences are in some sense authentic is whether the individual wants and values the effects of the PCE and whether the individual is autonomous in his or her decision to use PCE. This, we suggest, is a legitimate concern and is addressed in the following section.

COERCION

If PCEs were to become more commonplace, then employers might start to require their employees to use PCEs. The Academy of Medical Sciences et al. (2012) suggested in a recent report that "[O]ccupations that require particular patterns of focus could benefit from enhancements that facilitate achieving such patterns. For example, surgeons may need to be able to concentrate for extended periods, whereas other jobs such as air traffic control can require very rapid reactions during periods of relative uniformity. As an extrapolation to this, it is possible that in these high-responsibility occupations enhancement could be seen as a moral obligation, or even demanded by the public." (p. 38, for a discussion see also Maslen et al., in press). The US Airforce has already approved the use of modafinil by its pilots (Caldwell and Caldwell, 2005) and some medical practitioners are beginning to wonder whether enhancement might be required of them in the future (Rose and Curry, 2010). Writing in the Journal of Surgical Research, surgeons have suggested that the use of PCEs may come to be required practice. They say, "The prospect of fatigued surgeons taking a prescription drug, such as modafinil, to allow them to operate for longer, and possibly to a higher standard, is perhaps not as far-fetched as some may suggest. This drug has already been trialed in emergency physicians, when performing non-medical-related tasks at the end of a nightshift." (Warren et al., 2009, p. 168).

Further, the authors note that there are "useful and warranted forms of coercion" (p. 170) such as forcing surgeons to undertake hygiene practices such as handwashing prior to and during surgery. Given that this *coercion* is acceptable, they go on to ask, "What will our employers feel about a drug that makes us less prone to error, able to work longer hours, or to operate more efficiently? Employers are able to request certain behavioral standards from their employees, dictate rest periods, and insist on abstinence from certain drugs to ensure that their doctors perform well—will a day arise where they can recommend or even insist on surgeons being artificially enhanced? This may seem fanciful, but recent work has suggested that a mixture of napping and caffeine attenuates fatigue in interns and thus should be adopted by hospital administration. Why not other types of stimulant?" (p. 171).

The ethical objection often raised in this context is that, although it is thought to be reasonable to require certain things of employees, such as compulsory training and codes of conduct, requiring them to ingest psychoactive substances into their bodies is too demanding a requirement. It would require a compelling justification (perhaps pointing to the severity of harm that would be prevented through requiring enhancement) to trump the value we place on preserving the right individuals have to determine what happens to their bodies and minds (for discussion of the right to mental self-determination in relation to enhancement and other mental manipulation, see Bublitz and Merkel, 2014). As far as possible, this right should be preserved, and this is especially the case where there is not enough evidence about the harms to which an employer would be subjecting his or her employee. Neuroscientific evidence will have a large role to play in understanding the seriousness of any proposed requirement. In addition to the risks posed by individual instances of PCE use, more data on the potential for dependency will be essential for this discussion. Whilst we *might* think it permissible to require some employees to take small, isolated personal risks, requiring them to do something that results in substance dependency would more comprehensively infringe an individual's autonomy. In this connection, although PCEs may become more common in the workplace, one of us has argued elsewhere that for these and other reasons, it is unlikely that there will ever be a legal obligation for a professional like a surgeon to take a PCE (Goold and Maslen, 2014). At present, no employer requires employees to take caffeine. Caffeine is a PCE.

Even if people were not directly coerced to take enhancers it could still be objected that permitting PCE use could result in indirect pressure to use them. The perception that others are taking substances that make them more productive could lead to the belief that taking them is necessary to keep up (Academy of Medical Sciences et al., 2012) and not taking PCEs might render one *de facto* ineligible for certain jobs (Chatterjee, 2004). However, whether indirect pressure to take PCEs would in fact result in their more prevalent use is a question for social science. (For empirical data relating to this question, see Franke et al., 2011 and Maier et al., 2013). Neuroscientific research will have little to contribute to the debate about the limits of acceptable social pressure and restriction on employees' autonomy. However, as noted above, opposition to enforced PCE use is partly motivated by the current lack of evidence on long-term safety and efficacy. What we can legitimately require of people is closely related to what risks we can require them to take. Assessment of the legitimacy of requiring certain individuals to take PCEs will depend in large part on their medical safety and efficacy. If PCEs are very safe and efficacious, their use in life-saving/threatening professions (e.g., surgeons, politicians, truck drivers, airline pilots, etc.) may legitimately be required.

TREATMENT vs. ENHANCEMENT

As noted in the introductory section, there is much disagreement about what should count as enhancement (c.f., Parens, 1998). Sometimes this disagreement is framed as a debate about where *treatment* ends and *enhancement* begins. The distinction often made is that treatments serve to cure illness and preserve health whereas enhancements make people "better than well." For example, Juengst (1998) defines enhancement as the term "usually used in bioethics to characterize interventions designed to improve human form or functioning beyond what is necessary to sustain or restore good health" (p. 29).

However, a common objection to this distinction is that, in many cases, what we define as "healthy" and "normal" is arbitrary.

This objection does not deny that there can be clear failures of function or physiology as a result of pathology which most would agree are inimical to good health, such as the effects of a brain hemorrhage or stroke. Rather, it emphasizes that the boundary between healthy and unhealthy cognition in many cases is a matter of where we choose to draw the line, not based on either statistically significant subfunctioning or pathology. For example, delimiting normal from defective powers of concentration when diagnosing ADHD is necessarily to engage in marking a categorical point on what is otherwise a continuum (c.f. Schermer and Bolt, 2011). The point could be selected further to the left or right on that continuum of functioning. Would selecting a point which increased ADHD diagnosis increase the instances of individuals being treated or would some be receiving enhancement through the back door? Since the point is to some extent arbitrary, the corresponding labels of treatment and enhancement appear less meaningful in this context.

Similarly, it is difficult to know whether to classify substances used to combat age-related cognitive decline as instances of treatment or enhancement. Drawing sharp lines could have the result that a young person with cognitive abilities just above the cut off for being classified as having a mental disability would be "enhanced" by a drug but the elderly person whose abilities slipped to a level still above the young person would be receiving "treatment" if given the same substance (for a similar example, see Sandberg, 2011). Given the slipperiness of the distinction, one of us has argued (Savulescu et al., 2011) that instead of trying to determine whether certain drugs or certain of their effects constitute treatment or enhancement, it is more coherent and useful to think of a continuum of well-being which can be increased or diminished by various interventions.

It might be thought that evidence from neuroscience could adjudicate between instances of treatment and enhancement. If substances have discernable, discrete effects on different groups of people, it could be argued that these discrete effects mark the difference between a treatment and an enhancement. For example, although the way modafinil works is still unknown in detail (Minzenberg and Carter, 2008), neurologists do know that the brain of the narcoleptic is not neurophysiologically equivalent to the brain of the sleep-deprived individual and, correspondingly, it might be hypothesized that the effects of modafinil on the two groups will differ. Most forms of narcolepsy are associated with a deficiency in the hypothalamic neurotransmitter orexin (Mignot, 2010). The average sleep-deprived person, in contrast, does not exhibit such a deficiency. Accordingly, it might be thought that the more differences neuroscience can reveal between the narcoleptic and the non-narcoleptic, the better equipped we will be to distinguish between the treatment and enhancement effects of at least this PCE.

However, such knowledge would still not provide a definitive solution to which effects we should refer to as treatment and which we should call enhancement. Modafinil is also prescribed for shift work sleep disorder (SWSD), which is a product of unusual working patterns affecting circadian rhythms, not of underlying neurophysiology (Åkerstedt and Wright, 2009). This being said, it should be noted that not everyone who does shift work suffers from SWSD. This suggests that there must be some physiological or psychological difference between sufferers and non-sufferers and our lack of knowledge as to the cause of this difference does not make the disorder less of a treatable disorder.

In labeling the prescription of PCEs for SWSD an instance of treatment, a normative or ethical decision is still being made about which conditions and patterns of functionality should attract medical attention and resources. We are also implicitly making an assessment that medical treatment is the just and appropriate course of action for sufferers of the disorder, rather than prioritizing a change away from shift work. Neither the individual's underlying neurophysiology nor the particular mechanism of action of the substance tells us anything about whether this decision is the correct one.

One avenue through which neuroscience might illuminate the treatment vs. enhancement debate is by identifying pathology associated with mental or psychiatric disorders or limitations. So far, accurate tissue or cellular level pathological classification of psychiatric disease or disorder has eluded researchers. However, if psychiatric disorders could be characterized in the same way as neurological disorders, the presence of pathology would separate conditions which are diseases from those which constitute normal human variation.

Given that PCEs are not universally available through the healthcare system, individuals without conditions for which PCEs are approved would currently have to obtain them through other, unauthorized routes. This means that some people will have access to them but others will not. Even if PCEs were available on an open market, there could still be financial or other barriers to their accessibility. We discuss this issue and its potential implications next.

DISTRIBUTIVE JUSTICE

Society-level debates about PCE-related inequality consider *distributive justice*, and are related the question of whether PCEs will exacerbate existing socio-economic inequality. A common argument is that, as with many technologies, the rich and informed will have access to them whilst the poor and uninformed will not (e.g., Fukuyama, 2002). Assuming that cognitive enhancement confers some benefits, this will make those already at an advantage even better off. Whether this would in fact happen would depend on factors such as the affordability and accessibility of PCEs, as well as on the realities of their cognition-improving effects: the affordability and accessibility of PCEs will determine whether people are able to use them; the effects of the substances will determine whether they really put people who do so at an advantage. However, although there is the potential for PCEs to exacerbate unfairness if their distribution is unregulated, as one of us points out elsewhere, this is not a necessary consequence (Sandberg and Savulescu, 2011): if PCEs were distributed according to a principle of justice such as "prioritarianism"—the principle that says that we should give priority to those who are worst off, but also aim to maximize well-being of everyone in society—then PCEs would be most accessible to the worst off, becoming less accessible (but not inaccessible) as need decreases.

Further as we go on to discuss below in relation to competitive fairness, neuroscientific evidence supports the hypothesis

that there is a base-line effect of many PCEs: their effects seem to depend on the subject's baseline working memory capacity. Individuals with low working-memory capacity improve while high-span individuals are either not affected or are even impaired (de Jongh et al., 2008). This means that those most in need of PCE would benefit most from it, with those less in need not benefiting at all or even experiencing impairment from the same substance. Given this evidence, it has been suggested that enhancement might actually serve to *reduce* inequality (Bostrom and Sandberg, 2009). However, whilst this could be true in terms of the equality of cognitive capacity, it must be remembered that cognitive capacity and socio-economic status are not always correlated: there would still be people with more opportunities and resources who could improve their prospects further. Whilst policy decisions about access to PCEs will be principally socio-political matters, those making the decisions will need to know how enhancers affect members of the population in order to best serve the interests of justice and equality. If PCEs have differential effects on those who are already worst off, this will be highly relevant to their permissibility and just distribution. Neuroscience research can thus contribute to ethical debate if effects in targeted and specified populations of ethical significance are studied. This would require ethically relevant population stratification.

COMPETITIVE FAIRNESS AND CHEATING

The ethical discussion of whether using cognitive enhancers constitutes *cheating*—perhaps in exams or at work—is more nuanced than the simple question of whether taking enhancers is "against the rules." It can extend beyond considerations of *fairness in competitive contexts* to ask whether personal achievements facilitated by PCEs are devalued for this reason (c.f., Schermer, 2008; Goodman, 2010; Santoni de Sio et al., in press). We suggest that evidence from neuroscience will help to develop the cheating debate in important ways. Below, we argue that three types of empirical inquiry are relevant to the ethical discussion. The first, the phenomenon of the "inverted U"—according to which the enhancing effects of PCEs are often baseline dependent and exhibit non-linear dose response curves —(de Jongh et al., 2008; Husain and Mehta, 2011), is relevant to efficacy questions involved in debates about cheating. The second type of study relevant to the debate is that which seeks to identify the particular neural systems affected by different substances, leading to disparate effects (e.g., Lanni et al., 2008): whether a substance improves creativity or rote learning may matter for some possible conceptions of what constitutes cheating. Similarly, whether a substance improves motivation and task enjoyment vs. memory capacity might matter for those who place a lot of value on success requiring effort. Third, we argue that the neuroscientific evidence pointing to the likelihood of cognitive trade-offs (de Jongh et al., 2008; Husain and Mehta, 2011) adds an underdeveloped dimension to the cheating debate: if the complaint is that achievements facilitated by PCE are devalued because they do not involve enough personal sacrifice, then evidence suggesting that enhancement in some domains comes at the cost of impairments in others offers a challenge to this view.

The inverted U curve and baseline dependency

Neuroscientific research so far shows that the effects of many purported PCEs are base-line dependent and have an inverted U-shaped dose-response curve (de Jongh et al., 2008; Husain and Mehta, 2011). This is important to the cheating debate as it means that some individuals will benefit from taking PCEs whereas others will gain no benefit and might even be impaired: low performing individuals will tend to be on the upward slope of the inverted-U and so benefit from a substance that moves them further up this slope. High performing individuals, on the other hand, will tend to be at the peak of the inverted U and will therefore become impaired by a substance that increases neurotransmitter levels further. If neuroscience were to more precisely identify the neurological profiles of those who are able to benefit from PCEs and those who are not then ethicists would be able to consider in greater detail whether the prospect of some being able to enhance whilst others cannot counts more decisively against PCE in competitive contexts than if all could enhance in these contexts. They would need to consider whether it is the case that enhancement is only fair if everyone could (in principle) avail themselves of it or whether is it permissible given that some are physiologically denied the possibility of improving.

Disparate effects of different PCEs

Although the exact mechanisms of substances like methylphenidate and modafinil are not yet fully understood, researchers have begun to investigate which PCEs affect which underlying systems, and with which effects (Lanni et al., 2008; Smith and Farah, 2011). Although cognitive functions necessarily interact, attempts have been made to ascertain the primary cognitive functions improved by particular PCEs based on their effects on neurotransmitters. Husain and Mehta (2011) explain that "a simple mapping between a specific neurotransmitter and a particular cognitive function—such as [working memory]—[. . .] seems untenable. However, subtle but important differences in the precise processes modulated might provide some discriminating value: for instance, dopamine has an established role in reinforcement learning in response to rewards, whereas serotonin seems to modulate reinforcement learning for aversive stimuli." (p. 29). Pursuing such discrimination, Lanni et al. (2008) review the neuroscience literature investigating the neuronal circuits, neurotransmitters and molecular events underlying the cognitive domains of memory, attention, and creativity to distinguish the effects of different enhancement substances. Elsewhere, Smith and Farah (2011) review the cognitive neuroscience literature to examine whether (and which) prescription stimulants improve learning, working memory, cognitive control, and other executive functions.

If neuroscientific research were able to distinguish between the effects of different PCEs this could have some implications for discussions about cheating. This is again effect stratification. Combined with population stratification, neuroscience research could bring us closer to understanding what effect this particular PCE will have in this person. This reflects the move to "personalized medicine" and might be dubbed "personalized enhancement." Only when we can predict the *personal* benefits and costs of enhancement can policy be truly informed and ethical.

It might be thought that the enhancement of some cognitive functions is more unfair than the enhancement of others. For example, the enhancement of creative thinking might be thought to constitute more significant cheating than improving wakefulness or even memory capacity. Imagine someone who says "when I take enhancers my work is no better, I can just do more of the same for longer" vs. someone who says "when I taken enhancers my work is much better than I can do without them." Having links with the debate about authenticity, it is as if the former individual is enabled to make better use of his or her own cognitive resources, whereas the latter is given new cognitive resources upon which he or she can draw. Those who think PCE use is unfair because the achievement is not a reflection of the person's natural abilities to solve and create might be less concerned by a PCE that simply allowed more efficient work of the standard the person could naturally achieve. A PCE that promoted wakefulness might allow an individual to work for longer but it will not come up with ideas on his or her behalf. Of course, it is important to remember that a PCE that improved creativity still has its effects on and through the individual's own brain. What will be interesting for ethicists to discuss is whether "assistance" with time management and efficiency is relevantly different to "assistance" with the content of ideas (if, indeed, we want to characterize the respective effects in this way).

Practical consequences might be to consider certain substances unfair for certain types of tests or for entry into certain types of employment: employers might only be troubled by the use of PCEs, the effects of which are *necessary* to carry out the job. This would be a practical consideration: could the employee continue to work without the PCE? For example, an architect who could only perform satisfactorily when taking a substance like modafinil that seems to improves spatial planning and visual pattern recognition memory (Turner et al., 2003) might be thought to be a higher risk employee than one who uses a memory enhancer which enables him or her to remember the names of building materials that he could look up without problem in the absence of the substance.

Further, neuroscientific research that could distinguish between substances that enhance the *effectiveness* of cognitive capacities, such as working memory, from those that instead (or additionally) increase *motivation* could also have implications for the competitive fairness debate. In the ethical literature, the point is sometimes made that it is effort and striving that makes achievements intelligible and valuable. For example, Fox (2005) argues that "[b]ecause they act directly on the human body and mind, biotechnological enhancements tempt us to shirk individual striving and struggle" (p. 1150).

A common rebuttal to this type of argument is that, whilst PCEs can make efforts more effective, they do not replace the need for dedicated, sustained study—striving and struggle is still required in order to achieve. For example, Greely (2010) notes that "the more plausible cognitive enhancements would not eliminate the need to study; they would just make studying more effective" (p. 6).

If, however, there were a significant enough effect of a PCE on motivation and/or task enjoyment, then it would be open to ethicists to argue that this *does* in some sense reduce the amount of effort that the person puts in. The drive to work or achieve no longer emanates from the individual and no struggle is encountered.

On the motivating effects of prescription stimulants, Smith and Farah (2011) write: "Another empirical question concerns the effects of stimulants on motivation, which can affect academic and occupational performance independent of cognitive ability. Volkow et al. (2004) showed that [methylphenidate] increased participants' self-rated interest in a relatively dull mathematical task. This is consistent with student reports that prescription stimulants make schoolwork seem more interesting (e.g., DeSantis et al., 2008). To what extent are the motivational effects of prescription stimulants distinct from their cognitive effects, and to what extent might they be more robust to differences in individual traits, dosage and task? Are the motivational effects of stimulants responsible for their usefulness when taken by normal healthy individuals for cognitive enhancement?" (p. 735).

If particular PCEs were shown to significantly improve motivation and/or task enjoyment whilst others only improve effectiveness, ethicists would need to consider whether there is any relevant difference between enhancing motivation and enhancing effectiveness and, if so, what the implications would be for the value of resulting achievements.

Enhancement is likely to involve trade-offs

Research suggests that enhancing one domain of cognition might come at the cost of impairing another. de Jongh et al. (2008) review evidence suggesting trade-offs between long-term memory and working memory; between stability and flexibility of long-term memory; between stability and flexibility of working memory; and perhaps, they conjecture, between cognition and mood. If a PCE comes at a cost—and, especially, a mental cost—this could also add a new dimension to the debate about cheating and the value of achievements.

In terms of gaining an unfair advantage over others in exams and other competitive tasks, the trade-offs would be relevant if the test required exercise of *both* the enhanced and the impaired capacity. Whilst the individual gains some advantage in some parts of the test, he or she would be disadvantaged in other parts. More generally, neuroscientific evidence of trade-offs are interesting to the debate about fairness and the value of achievements because some of the objections rest heavily on the idea that using PCEs means that no sacrifice—usually conceived as sacrifice of time, energy or other opportunities—is made by the individual.

For example, Kass (2003) says: "Yet in those areas of human life in which excellence has until now been achieved only by discipline and effort, the attainment of those achievements by means of drugs, genetic engineering, or implanted devices looks to be "cheating" or "cheap." We believe—or until only yesterday believed—that people should work hard for their achievements. "Nothing good comes easily."" (p. 21).

If enhancement of one domain of cognition comes at the cost of another then it does seem that some sort of sacrifice has been made. We might conceive of an individual who chooses to enhance his or her working memory such that he or she can solve complicated puzzles quickly. This same individual might accept that this enhancement comes at the cost

of him or her finding it harder to recall facts and experiences from longer ago. Accordingly, whilst the physical act of ingesting a substance might be easy, there is a sense in which the enhanced capacity did not come easily—it did not come without personal cost. Whilst the conceptually most interesting trade-offs will involve impairments to cognitive capacities—like for like—it should also be noted that the more general side effects of PCEs (discussed in relation to medical safety above) also constitute an additional sort of "cost" to enhancement. The evidence on medical safety reviewed in section Medical Safety and Effectiveness suggests that PCE use will always come at a cost and may involve multiple costs of different kinds. The number and nature of these unavoidable costs constitute further challenge to the view that achievements facilitated by enhancement involve no sacrifice.

Important to note is that these costs of a trade-off are not like financial costs, which can be trivial and will constitute diminishment only insofar as they prevent the individual from making other purchases important to him or her. Rather, the costs of an enhancement trade-off are often mental costs—like for like—and are of a kind much more likely to constitute diminishment. Thus, neuroscientific research poses questions for those engaged in the cheating debate about whether there are relevant differences between different various costs of achievement—effort, opportunity, physiological side effects, cognitive trade-offs—and which (if any) are required for achievements to involve a sufficient level of sacrifice.

CONCLUSION

We have reviewed six of the main issues debated by ethicists working on PCE. Often, their purpose in debating these issues is to clarify concepts and normative positions, which then serve as a basis for recommending how society—and especially those tasked with its regulation—should respond to the emergence of PCEs. We have argued that whilst some of these issues are mostly political (coercion) or metaphysical (what constitutes authenticity), others have much to gain from emerging neuroscientific research. As well as providing data on safety and effectiveness, neuroscience will also allow a more fine-grained debate about whether the effects of some PCEs are more unfair than others in competitive contexts and whether employers should be more wary of employee reliance on some PCEs than on others. Further, due to emerging evidence on trade-offs, those who object to PCE on the ground that it facilitates individual gain without any attendant pain will have to explain why accepting an associated impairment in exchange for an enhancement is not a relevant sacrifice. Although we anticipate that ethicists will be far from stumped by this challenge, we hope to have demonstrated that it will, in large part, be though responding to emerging scientific evidence that normative accounts become more refined, complete and practically relevant.

In general, neuroscience can contribute to the formation of ethical policy on PCEs by adopting a "personalized" approach: personalized enhancement. Fine grained and stratified research should seek to identify specific risks, benefits, and trade-offs in small ethically relevant populations, or ideally in individuals. In doing this, according to the ethical values principles and criteria we choose, we can form policy on who should access which PCEs in which ways.

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When is diminishment a form of enhancement? Rethinking the enhancement debate in biomedical ethics

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The enhancement debate in neuroscience and biomedical ethics tends to focus on the *augmentation* of certain capacities or functions: memory, learning, attention, and the like. Typically, the point of contention is whether these augmentative enhancements should be considered permissible for individuals with no particular "medical" disadvantage along any of the dimensions of interest. Less frequently addressed in the literature, however, is the fact that sometimes the *diminishment* of a capacity or function, under the right set of circumstances, could plausibly contribute to an individual's overall well-being: more is not always better, and sometimes less is more. Such cases may be especially likely, we suggest, when trade-offs in our modern environment have shifted since the environment of evolutionary adaptation. In this article, we introduce the notion of "diminishment as enhancement" and go on to defend a *welfarist* conception of enhancement. We show how this conception resolves a number of definitional ambiguities in the enhancement literature, and we suggest that it can provide a useful framework for thinking about the use of emerging neurotechnologies to promote human flourishing.

Keywords: enhancement, neuroenhancement, welfare, well-being, neuroethics, bioethics, diminishment, empathy

INTRODUCTION

Advances in neuroscience and related fields have allowed for an unprecedented increase in our ability to intervene in brain-level processes, thereby influencing a wide range of higher-order functions and behaviors. As Nagel (2010) has noted, this growing and ever more finely-tuned capacity to tamper with even normally-functioning neural systems raises a number of ethical questions about the boundary between traditional research/clinical practice and outright human enhancement. "[A] societal climate of performance measurements and improvements," Nagel writes, has led to a "growing tendency to use medical and technological means beyond their applications in classical therapy" (p. 1). Hence, even though "most of these technologies are developed for medical or research purposes, their application for [human] enhancement interventions is at hand" (*ibid.*).

A burgeoning academic literature has begun to debate the moral propriety of such enhancement. This debate often centers on the use of neurotechnological, pharmacological, or other interventions to *increase* some human capacity or function (e.g., Bostrom, 2003, 2009; Bostrom and Roache, 2008; see also Daniels, 2000; Harris, 2007; and Kass, 2003a; especially pp. 12–13). What, after all, is the meaning of "enhance" if not to heighten, to augment, to intensify? Thus we see articles asking whether non-invasive brain stimulation should be used to enhance learning (e.g., Cohen Kadosh et al., 2012); whether we should be worried about university students taking Ritalin to improve focus (e.g., Outram, 2010); whether doctors have an obligation to ingest ergogenic drugs to stay awake during late-night surgery (e.g., Greely et al., 2008); and whether the use of mood brighteners is getting out of hand (e.g., Farah, 2002). The "augmentative" flavor of much of this work can be seen in a recent article by Dees (2007, p. 372):

> [Now or in the near future] drugs may be able to improve our ability to think. Amphetamines can help people to learn skilled motor tasks, like playing the piano, more rapidly. Cholinsterase inhibitors now help [patients] to improve their attention and memory, and better versions may help virtually anyone. Amphetamines, like Ritalin, improve focus, attention, and memory... Some drugs may help the formation of long-term memories and thereby facilitate learning... [Drugs can also] alter people's moods.... Soon drugs almost certainly will be developed that will "brighten" the mood of anyone who takes them.

Bostrom and Roache (2008) take a similar approach: "One important way in which the human condition could be changed is through the enhancement of basic human capacities... There are various ways in which we can currently improve [these capacities, including] stamina, strength, dexterity, flexibility, coordination, agility, and conditioning" (pages 1 and 7 [1]). In another paper, Bostrom (2009, p. 8[2]) asks us to

[1] Page numbers are from the online version available at http://www.nickbostrom.com/ethics/human-enhancement.pdf
[2] Page number is from the online version available at http://www.nickbostrom.com/ethics/dignity-enhancement.pdf

> Consider, for example, enhancements in executive function and self-control, concentration, or of our ability to cope with stressful situations; further, consider enhancements of mental energy that would make us more capable of independent initiative and that would reduce our reliance on external stimuli such as television; consider perhaps also enhancement of our ability to withstand mild pains and discomforts, and to more effectively self-regulate our consumption of food, exercise, and sleep.

Note the specific focus here on *capacities, moods,* or *functions* that might be improved by the pharmacological (or other) intervention—"improved" in the sense of facilitating *more* of whatever it is that the function normally does (see Dresler et al., 2013 for a recent review). We can summarize this sort of approach as follows:

> **The Functional-Augmentative Approach to Enhancement**: Interventions are considered enhancements insofar as they improve some capacity or function (such as cognition, vision, hearing, alertness) by increasing the ability of the function to do what it normally does.

The debate then typically turns on whether the proposed capacity-enhancement should be considered *permissible* for someone who does not suffer a "medical" disadvantage along that dimension (Daniels, 2000; Allhoff et al., 2009). In this context, a distinction is frequently drawn between "enhancement" (on the one hand) and mere "treatment" or "therapy" (on the other), with the implication often being that the former may be morally problematic in ways that the latter may not be. This consideration suggests a second approach to understanding enhancement:

> **The Not-Medicine Approach to Enhancement (Treatment vs. Enhancement)** (see, e.g., Sabin and Daniels, 1994; Juengst, 1998; Daniels, 2000; Kass, 2003b; Pellegrino, 2004): On this view, "the term *enhancement* [characterizes] interventions designed to improve human form or functioning *beyond what is necessary to sustain or restore good health*" (Juengst, 1998, emphasis added).

There are other approaches as well. In an earlier work, we identified two additional ways of understanding enhancement—the sociological-pragmatic approach and the ideological approach (see Savulescu et al., 2011, for details)—and then proceeded to outline a new account of enhancement, which we argued was preferable to the others: the welfarist approach. This approach can be defined as follows:

> **The Welfarist Approach to Enhancement:** "Enhancement" should be defined to mean any change in the biology or psychology of a person which increases the chances of leading a good life in a given set of circumstances.

In the present article, we wish to develop our defense of this welfarist account by contrasting it specifically with the "augmentative" functionalist approach [3] (i.e., enhancement of some capacity; see **Table 1** for a selective summary)—as well as the related "not-medicine" approach to enhancement—in light of recent discussions in neuroethics that seem to break the conventional mold. We introduce the notion of "diminishment as enhancement" and focus on a set of cases in which "subtractive" interventions—that is, interventions geared toward *weakening* a given capacity or function—might plausibly contribute to individual welfare enhancement in line with the definition just laid out. We conclude by discussing some of the advantages that this welfarist conception has over other common definitions.

DISCUSSION

What do we mean by "diminishment"? We can dispense with a potential red herring. We do *not* mean to draw attention to specific neural pathways or low-level mechanisms whose weakening or disruption might go on to yield some higher-order functional outcome. For instance, stimulants such as Ritalin, sometimes used to augment focus and concentration, could in principle be understood as "diminishments" since—on at least at one level of description—they actually *limit* the reuptake of neurotransmitters, ultimately producing their stimulating effects [4] . Likewise, TMS and other forms of brain stimulation may involve *disrupting*

[3] One may wonder just how common this approach is—that is, how frequently it is encountered in the literature compared to other approaches. As noted above, in addition to the work of prominent figures such as Bostrom—who define enhancement explicitly in terms of augmentation of functions or capacities (see especially Bostrom, 2009)—the most commonly referenced account is the "not-medicine" approach, which distinguishes enhancement from treatment, as in the seminal report from the President's Council on Bioethics, "Beyond Therapy" (Kass, 2003b). "Therapy" is ordinarily understood as being an attempt to address disease, which on the dominant account after Boorse (1977) is species-typical subfunctioning (see also Daniels, 1985). Therefore, on the "not-medicine" approach as well, enhancement just is the improvement of some function within (or beyond) the normal range. We do not suggest, of course, that the functional-augmentative view is the only view one encounters in the literature, nor that cases of functional diminishment are never employed in these debates. Indeed, one of the classic examples of "enhancement" from the field—the blunting of painful memories (which we discuss below)—is quite common. However, in our reading of the literature, it is examples relating to capacity augmentation that are much more frequently encountered and actually used as illustrations of enhancement; and when instances of diminishment are raised, their specific implications for the conceptual understanding of enhancement is rarely if ever addressed. In addition, the link between the intervention (whether augmentative or diminishing) and *well-being* is not commonly articulated as such, with other goals such as "self improvement" being either stated or implicitly assumed (e.g., Farah, 2013).

[4] Though note, as a reviewer points out: diminishment-as-enhancement "can work at both lower (neurobiological) and higher (mental, psychological) levels in a complementary way [depending upon the way the enhancement is described]. While methylphenidate produces its stimulating effect by limiting the reuptake of dopamine, it enhances one's capacity to be more attentive to and focused on a particular task by diminishing the content and scope of one's attention" (emphasis added). Thus we can see that it is possible to augment (via diminishment) a given capacity (here, focus), not only by interfering with some lower-order neurological process, but even by diminishing an inversely related higher-order capacity: in this example, the scope of one's attention. Therefore it is important to make clear (as we do in a subsequent paragraph) that our emphasis in this paper is on interventions that would diminish the targeted higher-order capacity itself (i.e., focus), rather than either (a) some lower-order mechanism whose diminishment would actually

Table 1 | Selective summary of "augmentative" neural enhancements, means, and references.

Function	Means	References
Attention	Nicotine, Modafinil, caffeine, glucose, aerobic exercise, rTMS, computer training, meditation	Benton et al., 1994; Hilgetag et al., 2001; Rezvani and Levin, 2001; Newhouse et al., 2004; Repantis et al., 2010; Smith et al., 2010; Chiesa et al., 2011; Zelinski et al., 2011
Empathy and mind-reading	Oxytocin, MDMA	Bartz et al., 2010; Hysek et al., 2012
Executive function	Aerobic exercise; computer training; meditation	Smith et al., 2010; Chiesa et al., 2011; Nouchi et al., 2012
Learning—including implicit learning, verbal learning, and numerical learning	Amphetamine, methylphenidate, a large number of synaptic-plasticity affecting drugs, tDCS, various memory arts and mnemonic systems	Soetens et al., 1993; Clark et al., 1999; Kincses et al., 2004; Williams and Eskandar, 2006; Lee and Silva, 2009; Cohen Kadosh et al., 2010; Repantis et al., 2010; Javadi et al., 2012; Suthana et al., 2012
Inhibitory control and self control	Modafinil, Atomoxetine, glucose	Turner et al., 2003; Galliot et al., 2007; Chamberlain et al., 2009
Memory—including working memory, memory encoding, and memory consolidation	Glucose, donepezil, physiostigmine, exercise, tDCS, Ampakines, Modafinil, methylphenidate, computer training, protein, meditation	Elliott and Sahakian, 1997; Furey et al., 2000; Lynch, 2002; Turner et al., 2003; Barch, 2004; Marshall et al., 2004; Fregni et al., 2005; Luber et al., 2007; Jaeggi et al., 2008; Ohn et al., 2008; Riby et al., 2008; Thorell et al., 2009; Smith et al., 2010; Chiesa et al., 2011; Teo et al., 2011; Jones et al., 2012
Planning	Methylphenidate	Elliott and Sahakian, 1997
Reaction speed	Glucose	Owens and Benton, 1994
Recall	tDCS	Gagnon et al., 2010; Ross et al., 2010
Wakefulness/alertness	Caffeine, Modafinil, amphetamine, other stimulants	Hartmann and Cravens, 1976; Smith, 2002; Baranski et al., 2004

activity in one region as a means to enhancing function in another (or at another level of description). For example, TMS can reduce interference between similar-sounding words in phonological memory (likely by disrupting the phonological store), thereby improving verbal recall (Kirschen et al., 2006). In these sorts of cases, it is the higher-order function itself that we take to be the target of enhancement (i.e., the capacity for focus, concentration, or recollection), whereas the lower-order "diminishment" is merely instrumental.

By contrast, we intend to highlight interventions that serve to diminish the higher-order capacities themselves. That is, we want to focus on interventions that make concentration (for example) *worse*—by virtue of *whatever* neural mechanism is involved. Consider some illustrative cases. Should soldiers be given propranolol to *reduce* the emotional intensity of wartime memories (e.g., Henry et al., 2007)? Should a battered spouse use "anti-love" neurotechnology to *sever* the emotional attachment she has with her abuser (Earp et al., 2013)? Should sex offenders have to undergo "chemical *castration*" as a condition of parole (e.g., Gupta, 2012)? Should appetite *suppressants* be developed for mass-market consumption (e.g., Farah, 2013)? These are just a few recent examples of potential interventions that might reduce or diminish a higher-order capacity.

Interventions of this kind raise many of the same patterns of ethical concern as the more conventional cases of functional enhancement typically encountered in the bioethics literature. For example: who should administer the drug or apply the technology? Should the intervention be regulated? How? Is a threat to autonomy or authenticity potentially implied? And what sort of externalities might need to be anticipated?

At the same time, however—given a functional-augmentative framework—these cases might seem puzzling or out of place. They seem puzzling because they apparently involve the very *opposite* of enhancement, namely, diminishment: i.e., *diminishment* of wartime memories; *diminishment* of harmful love; *diminishment* of ill-directed lust, and so on. How might these seemingly opposite-to-enhancement outcomes be made to square

increase the target capacity, or (b) an inversely-related higher-order capacity, whose diminishment would have a similar effect.

with the seemingly similar-to-enhancement applicability of "standard" bioethical analysis?

There is a straightforward solution to this puzzle. Sometimes, diminishment *is* enhancement—on the welfarist definition of the term (see above). That is, once we shift our focus from the particular *capacity* or *function* being modified to the overall *normative goal* of the modification itself, we begin to see that "enhancement" may be more broadly understood as having something to do with well-being—a goal that the welfarist definition makes explicit. On this account, in order for an intervention to count as an enhancement, it does not matter if the capacity itself is being modified "up" or being modified "down." Nor does it matter if the modification is being accomplished by means[5] of a drug, a biochip, an electrical brain-stimulator, or something more familiar and lower tech. Nor does it matter if the intervention is called "medicine" or "therapy" or "beyond therapy" or anything else. If it increases the person's chances of leading a good life in the relevant circumstances, then we propose that it should be considered an enhancement.

IMPLICATIONS OF THE ARGUMENT

Well... so what? What does this welfarist definition get us? How will it be *useful* for medical professionals, neuroethicists, and other stakeholders engaged in these sorts of discussions? Finally, what advantages does it have over other definitions used throughout the literature?

First, and most basically, it acknowledges that "more" is not always "better." As commonplace a maxim as this is, it is not always duly appreciated. As the neuroscientist Baron-Cohen (2011) has recently argued, even such "obviously" beneficial human capacities as the ability to empathize may have maladaptive consequences in certain cases. For example, too much empathy might drive a person to prioritize attending to others' feelings over meeting her own basic needs. Or consider "empathy fatigue"—a term used by Stebnicki (2007) to refer to the physical and emotional exhaustion that grief and trauma counselors sometimes come to face: their inability to *distance* themselves emotionally from the pain and suffering of their clients ultimately prevents them from doing their job. Likewise, Williams (1989) has hypothesized that among helping professionals, high emotional empathizers may be disposed to earlier career burnout.

The same lesson may apply to other "obviously" beneficial capacities such as intelligence or IQ. While super-intelligence might seem to be an enviable trait or disposition, being "too smart for one's own good" is not always a mere teasing admonition: for many intellectually gifted individuals, very high intelligence can come at a direct cost to their overall well-being (Harrison and Van Haneghan, 2011). Furthermore, intelligence is not sufficient for achieving the good life, but is merely instrumental, and IQ enhancement *per se* does not seem to have any clearly determinate value (Tännsjö, 2009).

Likewise, the ability to remember well would seem to be a beneficial thing: "memory makes us" (it has been said) and many elderly people are very sad to see their powers of recollection fade over time. But as any victim of rape might tell you—and as the soldiers we referred to earlier would hasten to agree—sometimes memory can be a devastating shackle. In addition, research has shown that excessive autobiographical memory (hyperthymesia) can interfere with the basic business of living one's life (Parker et al., 2006).

Finally, even romantic love—undoubtedly the most celebrated emotional capacity of all—can be dangerous or even life-threatening when the object of affection is cruel or abusive. Some victims of domestic violence, for example, find themselves unable to diminish their passionate feelings for their abuser, despite being fully aware that their long-term well-being and even basic physical safety may be under threat by remaining in the relationship (Earp et al., 2013, 2014, under review; see also Earp et al., 2012, for further discussion).

The implication in all of this is clear; and here we reaffirm our thesis to drive it home: Sometimes, diminishing a certain *capacity* or *function*—under the right set of circumstances—could quite plausibly *enhance* a person's overall well-being.[6]

SOME FINE-TUNING

Given this possibility, one might be tempted to argue that functional diminishment would only enhance well-being by bringing the individual back from a *pathological* state to a species-typical state. Yet while this direction of change could reasonably describe a number of specific cases, it is unlikely to hold as a general rule. This is because what it is that enhances well-being is not species-general, but rather context-specific. Thus, as Dees (2007) notes, "beta blockers [can be used to] decrease stress and nervousness, and so they help even normal people cope with abnormal situations" (p. 372). In the context of a public performance, for example, even a quite ordinary stress reaction could interfere with an individual's well-being, given the context-local goals of the performer: hence "[the] widespread use [of beta-blockers] among concert performers is legendary" (*ibid.*) Likewise, in the notorious "Ashley case" (Liao et al., 2007), the parents of a severely brain-impaired child wanted to stunt her growth by using estrogen therapy (as well as remove her uterus and breast buds) in order to improve her quality of life. While parts of the treatment and even the motivations behind it may certainly be called into question, it is at least plausible to think that reducing Ashley's growth, all things considered, would count in favor of her own best interests. For example, Ashley's parents suggested that her smaller size would make it easier to carry her around, thus allowing her to participate more fully in the activities of daily living. If so, then approaching the normal human size range would *not* improve well-being, whereas the proposed diminishment might.

[5]Note that the means "do not matter" only in the specific sense stated—i.e., in terms of whether some intervention should be counted as an enhancement. By contrast, the means might very well matter in terms of having different safety profiles, etc. Furthermore, there is no reason to think that all means will be normatively equivalent either, even if well-being is taken as the explicit goal of enhancement. This is because there are other normatively-relevant considerations besides well-being, such as justice or fairness, which may impact upon the evaluation of means (as well as other factors related to enhancement), as we discuss in a later section.

[6]This sort of welfare enhancement is likeliest to occur, we suggest, when the functional diminishment in question results in optimal levels of capacity functioning for successful adaptation to the demands of the environment.

But what is the more general thrust of the argument? In other words, when, or under what conditions, is (functional) diminishment likely to produce (well-being) enhancement? We have already discussed context-specific and "pathological" cases, but others suggest themselves as well. One plausible view is that we should expect promising enhancers when the trade-offs in our living conditions have shifted from the environment of evolutionary adaptation (Bostrom and Sandberg, 2008). While some changes no doubt enable well-being enhancement in the sense of getting *more* of something that was limited in the past because of its cost, there are likely other domains in which something has lost importance today. For example, fight-or-flight reactions that would have served well in an environment flush with predators might today contribute more to stress, cardiovascular disease, and problems with anxiety (Bracha and Maser, 2008). Anti-parasite immune cells can become overactive in our relatively clean environment, triggering allergies (Sironi and Clerici, 2010). And ancient hunger drives can lead to obesity in today's societies, given the unprecedented availability of low-nutrient, high-calorie foods (e.g., Serlie et al., 2011). These examples provide further potential cases in which we might judiciously *diminish* our body's natural responses in order to improve our overall well-being.

CONCLUSION

Our aim in this article has been simple. It has been to rethink, or at least to problematize, the chiefly "augmentative" flavor of discourse surrounding neurotechnological enhancement. We do not mean to imply, of course, that all or even most of the diminishments we have discussed are currently technologically feasible, nor do we suggest that they would always be the best solution to the problem at hand. As Levy (2012) has recently argued, when faced with a detrimental mismatch between our capacities and our context, it is often better to change our environmental conditions than it is to re-tool our biology, all things considered. Other times, the best course of action might be to pursue a complementary strategy that involves the use of brain-level interventions alongside other types of approaches (Savulescu and Sandberg, 2008). The answer is likely to be different for different cases.

Yet whatever position one takes on the proper balance of intervention strategies, we have tried to show that there is something to be gained by distinguishing functional enhancement from enhancement of well-being. For any disposition, trait, or function, there is likely to be a discrete range of optimal levels (of intensity, sensitivity, etc.) for the given set of conditions, and too much or too little may detract from health or happiness. Identifying diminishment as a possible form of human enhancement, therefore, invites us to ask whether we may have *too much* X for the best life, based on the relevant local circumstances and other facets of modern living.

Another advantage of the welfarist definition of enhancement is that it can handle not only cases of functional diminishment (our emphasis in this paper), but even unusual cases including *extensions* of the body, in which a new capacity is added that did not exist before. One example of such a case is the use of implanted magnets for "magnetic vision" (Larratt, 2004). While this type of intervention is clearly "augmentative" (in the sense of adding something rather than subtracting), it differs from the usual augmentative cases—which involve intensifying an existing capacity—in that it introduces a novel capacity that would not exist at all without the enhancement. Similarly other forms of body-modifications may be seen as attempts to enhance well-being through bringing the body more in line with personal ideals of self-expression. These cases, too, may not involve the "enhancement" of any existing capacity, but rather welfare enhancement more broadly construed through the employment of biotechnology.

We are careful to note that we have left untouched important questions about who would administer these new technologies, under what specific conditions; how their advisability would be decided upon (especially as compared to other, potentially less invasive, forms of intervention); how long their effects should be expected to last; what risks or side-effects might be involved; and whether any regulatory structures would have to be put in place to accommodate their existence. These types of questions are bound to overlap with analogous puzzles being worked out in the "augmentative" enhancement literature, so we will leave their discussion for another day. Here we have endeavored, not to cultivate a vast procedural forest, but rather to plant a conceptual seed.

FINAL THOUGHTS

As we have argued elsewhere (Savulescu et al., 2011), the "enhancement debates" in biomedical ethics have been needlessly encumbered by the existence of a hodge-podge of ill-defined, poorly articulated notions of enhancement—often only implicitly communicated—along with endless to-ing and fro-ing about the relationship between enhancement and the limits of medicine. Re-casting "enhancement" as being essentially related to welfare, however, provides several distinct advantages:

> It ties enhancement to the value of well-being... It offers a general framework for thinking about well-being. It offers more than a mere list of value claims. It singles out well-being as one dimension of value that is constitutive of genuine human enhancement. But it leaves open substantive and contentions questions about the nature of well-being, and important empirical questions about the impact of some treatment on well-being. [Moreover], the welfarist approach distinguishes ways in which some treatment might benefit a person from other relevant values, such as justice. It thus allows us to say that although some treatment is an enhancement (i.e., contributes to individuals' well-being), it might nevertheless be bad overall, because its employment in the current social context will lead to far greater injustice. (p. 7)

Finally, we note that people's normal brain functions will differ across time and circumstance. They will differ between people as well. We can now *control* function, at least in part, through the use of neurotechnology and biomedicine, and our ability to do so is likely to become increasingly more potent as well as more targeted in the decades to come. We suggest that we should tie this ability to a robust account of well-being (e.g., Kahane and Savulescu, 2008; Earp et al., under review), and seek to maximize function toward that end, whether the capacity itself is being augmented (as is typically emphasized in these debates) or indeed (as we emphasize here) effectively diminished.

AUTHORS' CONTRIBUTIONS

Brian D. Earp wrote the first draft of the essay, and undertook final edits to synthesize the contributions of the other authors. Anders Sandberg provided some of the scientific examples, and drafted the argument about shifting evolutionary trade-offs. Guy Kahane contributed substantial intellectual content and edited and approved the final draft. Julian Savulescu conceived the general argument and contributed substantially to the concluding paragraphs.

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When "altering brain function" becomes "mind control"

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Functional neurosurgery has seen a resurgence of interest in surgical treatments for psychiatric illness. Deep brain stimulation (DBS) technology is the preferred tool in the current wave of clinical experiments because it allows clinicians to directly alter the functions of targeted brain regions, in a reversible manner, with the intent of correcting diseases of the mind, such as depression, addiction, anorexia nervosa, dementia, and obsessive compulsive disorder. These promising treatments raise a critical philosophical and humanitarian question. "Under what conditions does 'altering brain function' qualify as 'mind control'?" In order to answer this question one needs a definition of mind control. To this end, we reviewed the relevant philosophical, ethical, and neurosurgical literature in order to create a set of criteria for what constitutes mind control in the context of DBS. We also outline clinical implications of these criteria. Finally, we demonstrate the relevance of the proposed criteria by focusing especially on serendipitous treatments involving DBS, i.e., cases in which an unintended therapeutic benefit occurred. These cases highlight the importance of gaining the consent of the subject for the new therapy in order to avoid committing an act of mind control.

Keywords: philosophy of mind, ethics, neurosurgery, deep brain stimulation, psychiatry

INTRODUCTION

The use of deep brain stimulation (DBS) technology for the treatment of psychiatric disorders is one of the most promising and rapidly evolving areas of neurosurgical research (Abelson et al., 2005; Mayberg et al., 2005; Lozano and Lipsman, 2013). Nonetheless, in treating diseases of the mind by directly altering the brain's functioning, neurosurgeons, neurologists, psychiatrists, and neuro-engineers run the risk of having this effort interpreted as "mind control". The purpose of this paper is to address that specific concern in the context of DBS as it is currently practiced and studied by providing a definition of "mind control" that applies to DBS. That is, it is not intended to account for the neurosurgeons staffing the wards of philosophical thought experiments, whose powers to monitor and manipulate the brain and their patients' actions know no limits (Frankfurt, 1969). Therefore, this paper seeks to cover adult patients who have given informed consent for the treatment of their psychiatric or neurologic illness.

By narrowing the scope of the article, we hope to maximize its relevance while minimizing distracting (though philosophically interesting) cases. It is important to point out that the conditions under discussion (adults, undergoing treatment, who are capable of informed consent—including patients in states such as locked-in syndrome) describe nearly all individuals currently receiving DBS with the exception of those treated for persistent vegetative state who lack the capacity to do anything, including the ability to provide consent (Yamamoto et al., 2010).

While the phrase "mind control" appears in the contemporary literature discussing advances in DBS, it is often brought up dismissively (Fins et al., 2009) or to catch the reader's attention (Horgan, 2004) but never with an accompanying formal definition. This is surprising, especially given a sophisticated and robust ethics literature on DBS and psychiatry that deals with related topics such as autonomy and informed consent (Bell et al., 2009; Clausen, 2010), authenticity (Kraemer, 2013), enhancement (Earp et al., 2014), and paternalism (Sjöstrand and Juth, 2014) as well as unintended side effects of stimulation which alter personality (Synofzik and Schlaepfer, 2008) and the way in which DBS can influence patients' perceptions of their identity (Lipsman et al., 2009). Common features in this literature are an agreement that autonomy is one of the key features that must be preserved in the ethical practice of DBS and that this can been accomplished in psychiatric patients through the practice of informed consent (Dunn et al., 2011).

Beyond the contemporary neuro-ethics literature, mind control has been the subject of numerous books and articles. One of the most thorough accounts of mind control in the context of electrical stimulation of the human mind appears in Elliot Valenstein's aptly titled *Brain Control* (Valenstein, 1973). While Valenstein never supplies a formal definition of mind control, his primary argument focuses on discrediting the notion that a subject's thoughts, choices or actions could be manipulated through electrical stimulation of the brain by giving a detailed account of its known capabilities and limitations. Other discussions of mind control tend to

have focused on psychopharmacologic methods or behavioral methods of altering brain function, such as those employed in the Central Intelligence Agency's MKULTRA program (Senate, 1977).

Possibly the richest source of accounts of mind control is not in the formal academic literature but in the online accounts of individuals who claim to have witnessed acts of mind control or who claim to be the target of mind control. In 2006 Bell et al. provided a formal textual analysis of 10 characteristic examples. Though the authors make it clear that they take these narratives as signs of a delusional disorder and their analysis focused primarily on the social network of the reports, they managed to highlight several themes which the accounts shared. These shared features help to establish an intuitive basis for what people believe qualifies as mind control. The accounts often focused on: (1) an authoritarian organization, such as "the police," "the Dutch government," or "freemasonic intelligence agencies;" (2) employing some tool to augment brain function, such as a "frequency weapon," "brain implant" or "network of transmitters," in order to; (3) alter the subject's thoughts or actions; (4) without the subjects consent.

In proposing our criteria for mind control we retained and formalized all of the common themes of the internet accounts with the exception of the authoritarian organization. The authoritarian element was dropped because the authors saw no reason to exclude individuals acting alone from being capable of committing an act of mind control. This is especially true in the context of DBS where typically only one person or a few people are responsible for the management of the treatment. Therefore, we are proposing the phrase "mind control" be used to describe instances when researchers or clinicians using DBS intentionally alter patients' behavior without consent and define those instances using the criteria below.

After stating our formal criteria, we explain why the criteria are limited to the subject's behavior and neutral with regards to the subject's mental events during the act of mind control. Then we provide test cases, which we argue intuitively do and do not qualify as mind control and are correctly included and excluded by the proposed criteria respectively. Next, we apply the criteria to a non-obvious case of mind control. Finally, we conclude with a discussion of mind control in the context of serendipitous therapy, i.e., cases where an individual sees a therapeutic effect for a psychiatric illness for which he or she did not give consent to have treated, such as in a patient treated with DBS for anxiety who saw a remission of his alcoholism. We argue that in such cases one should gain the individual's explicit consent for the treatment of the serendipitously improved comorbid illness or else one would qualify as committing an act of mind control.

CRITERIA OF MIND CONTROL

Alteration of the brain's functioning through direct stimulation (either activation or suppression of action potentials) within the subject's brain qualifies as mind control when it meets all of the following three criteria:

Result Criterion: Direct alteration of the brain's function must result in a behavioral change in the subject.

Consent Criterion: The behavioral change does not need to be against the expressed will of the patient. The change must simply have taken place without the subject's consent.

Intent Criterion: The behavioral change must have been the goal or the purpose of the person or the group controlling the DBS. It cannot be an accident or an unintended consequence, including side effects, of the stimulation.

In summary, mind control must alter the patient's behavior in an observable way without the subject's consent and must be enacted for that purpose.

LIMITING MIND TO BEHAVIOR

The above criteria rest on an assumption that the ultimate purpose of "mind control" is to modify the behavior of an individual, and the word "mind" is used in a folk psychology manner to describe the intuitive mechanism of the control (Dennett, 1982). It is important to spell out the definition of "mind control" in the context of behavior because that is the relevant way DBS is currently employed. This is because neurosurgeons and neurologists cannot make perfectly reliable *a priori* guesses about what effect a given instance of DBS will have on a given patient. They must therefore rely entirely on their observations of the patients' behaviors, which include their patients' reports.

To understand this point, consider that neurosurgeons have a great deal of information about what parts of the brain are associated with certain faculties, such as the formation and comprehension of speech, sensation of touch over the body, execution of intended movement, and sight. Further, they know that the destruction of these regions will leave the patient with a deficit so protecting them during surgery is one of the surgeon's highest priorities. However, the surgeons cannot predict exactly where these regions are located in specific patients based on previous studies alone (Penfield and Perot, 1963; Kim et al., 2009). Therefore, some neurosurgical cases are performed with the patient awake so that he or she can report the sensations he or she experiences when the neurosurgeon applies electric current to the brain region of interest. Based on the patient's reports, the surgeon will individualize his approach in order to resect the pathological tissue while sparing the functionally important, so called eloquent, cortex. If the procedure were performed without the patient's behavioral feedback there would be a very high probability that an important cortical region would be damaged leaving the patient with a neurological deficit (Penfield and Boldrey, 1937).

The same type of procedure is also essential to the practice of DBS. For example patients must be closely observed intraoperatively for behavioral signs, such as a reflexive smile, in order for the surgical team to determine the effect of stimulation (Okun et al., 2004; Haq et al., 2011). Once the electrode and stimulator are implanted, specially trained neurologists adjust the stimulation parameters and closely observe the effect on the patient's symptoms (Volkmann et al., 2006). Finally, patients must be closely followed during treatment for signs of cognitive decline (Parsons et al., 2006), mood disorders (Bejjani et al., 1999; Kulisevsky et al., 2002), or other, sometimes serendipitous, behavioral changes (Kuhn et al., 2007). In summary, the use of DBS relies entirely on the patient's behavior as the sole feedback mechanism

for targeting the electrode as well for modifying the stimulation parameters in order to achieve the desired effect. Because the person or persons controlling the DBS rely on observation of behavior, any instance of mind control using DBS would necessarily rely entirely on the subject's behavior. Therefore, a practical definition of mind control can be limited solely to behavior without directly addressing metaphysical questions related to the mind itself.

OBVIOUS TEST CASES

Having proposed the criteria for mind control, it is important to test them. This is best done by asking whether the criteria account for cases of obvious mind control while excluding cases that are obviously not mind control.

For a clear example of mind control, we must (fortunately) look beyond the current practice of DBS into its murkier past. One such case was published in 1963 in the journal *Science* by a psychosurgery group working under Dr. Robert Heath at Tulane University (Bishop et al., 1963). This article detailed a "self-stimulation" experiment in which a 35 year old man was implanted with electrodes in eight different brain structures, including in the head of the caudate, the septal area, and the amygdala. These electrodes were labeled by researchers as either "rewarding" or "aversive" and the subject was given a lever and a button which, when operated, would activate one of the electrodes. As the experiment proceeded, the researchers varied the electrodes which the lever and button activated and also varied the stimulation parameters delivered through the electrodes.

This experiment was based on studies previously done in rats, cats, dogs, goats, monkeys, and bottle nosed dolphins (Olds, 1962) which had shown that the animals' behavior could be predictably controlled by placing stimulating electrodes into "rewarding" and "aversive" regions of the brain and then correlating stimulation through the electrodes to elements of the animals' environment. Therefore, the researchers had good reason to anticipate specific behavioral responses in the human subject. Further, at no point do the authors say that the subject, who was referred to as "clearly nonnormal," gave consent for the experiment or understood why the experiment was conducted.

Looking back to the proposed criteria for mind control, we see that this case satisfies all three. First, electrical stimulation of the brain was employed in a manner that clearly influenced the subject's behavior, satisfying the *Result Criterion*. Second, at no point did the authors state that the patient gave consent to have his behavior manipulated in this manner, satisfying the *Consent Criterion*. Finally, the behavior change was anticipated by the researchers controlling the stimulation of the subject's brain, satisfying the *Intent Criterion*.

Next, we must ask is there an example of altering brain function which obviously is not mind control and, also, is correctly excluded by the *Result, Consent*, and *Intent Criteria*? Consider the treatment of essential tremor with DBS. It is safe, effective, and has been approved by the FDA (Koller et al., 2001). It is believed to work through altering the function of the brain (more specifically by causing a reversible, functional lesion (Grill et al., 2004) in a malfunctioning part of the brain), ultimately permitting the patient to accomplish routine daily activities free from the violent hand tremors that are the hallmark of the disease. This relief of symptoms is the direct result of the electrical pulses in the brain, which alter its standard pattern of firing; however, it is not an instance of mind control.

Why is DBS for the treatment of essential tremor not an example of mind control? After all, it could be argued that one is altering the behavior of the patient's hands, from a tremulous grasp to a stable grip, and that this was explicitly the purpose of the individual programing the DBS device. However, while this example meets the requirements of the *Result Criterion* as well as the *Intent Criterion*, it fails to meet the *Consent Criterion* because in all cases of DBS for essential tremor, all patients give consent for stimulation with the explicit desire to see this behavioral change. Interestingly, DBS for essential tremor could be thought of as "mind freedom," as opposed to "mind control" because, instead of preventing the patient from carrying out a desired behavior or forcing an undesired behavior, it allows the patient to act on his choices with less difficulty.

The same argument also holds for DBS treatments of psychiatric diseases like depression (Lozano et al., 2008). One might make the argument that being a psychiatric disease, depression is classically described as a disease of the mind. Therefore, if one can control the patient's disease one must be controlling the patient's mind, i.e., committing an act of mind control. The proposed criteria would exclude this case of mind control because, as in the case of DBS for the treatment of essential tremor, the effect on the patient was with the patient's consent, and, thus, it fails the *Consent Criterion*.

NON-OBVIOUS TEST CASE

While it is important that the criteria capture one's intuition, they should also go beyond and clarify murkier territory. The criteria should be able to help one examine non-obvious cases and arrive at a reasoned judgment about their status as mind control or as non-mind control. Thus, the criteria above are especially useful when attempting to identify borderline instances of mind control.

Turning again to the past, consider the following case of an experiment conducted by Jose Delgado and his collaborators Drs. Obrador and Martin-Rodriguez into the stimulation of the caudate nucleus of an epileptic patient:

> As shown by direct observation and by analysis of the record, within 30 s after application of caudate stimulation there was a significant change in the patient's mood. During controls, he was reserved, his conversation was limited and he was concerned about his illness. After caudate stimulation, his spontaneous verbalization increased more than twofold and contained expressions of friendliness and euphoric behavior which culminated in jokes and loud singing in a gay *cante jondo* style, accompanied by tapping with his right hand, which lasted for about 2 min. The euphoria continued for about 10 min and then the patient gradually reverted to his usual, more reserved attitude. This increase in friendliness was observed following three different stimulation sessions of the caudate, and did not appear when other areas were tested (Valenstein, 1973).

In the above description, the researchers are attempting to correct the patient's epilepsy with the use of electrical current. In testing one of their hypothesized targets, they managed to elicit a strong behavioral effect. The patient's attitude changed from quiet reserve to expressive joviality, i.e., the researchers significantly altered the patient's behavior and in doing so satisfied the *Result Criterion*, as well as the *Consent Criterion* because they did not have the patient's consent to alter his behavior in this manner. At this point one could argue, correctly, that this was an accident. The experimenters had no *a priori* knowledge that the patient would respond to stimulation in this fashion so it could not have been their intention to do so; thus, they failed to satisfy the *Intent Criterion*.

The essential issue arose when the stimulation was repeated, three different times, without any documentation that the patient wanted to have his personality manipulated in this manner. While this might, at first, seem like nit picking, it is important to appreciate that the experimenters now had reason to believe that the behavior of the individual would be affected in a specific way. When they activated the stimulation and produced the anticipated effect, it was purposeful. In this way, the experimenters fulfilled the *Intent Criterion*. As in the case of a schizophrenic patient subjected to the self-stimulation experiment above, it seems clear that the researchers' motivation was intellectual curiosity and not malice. Nevertheless, both of these cases demonstrate that malice is not necessary for mind control.

SERENDIPITY AND MIND CONTROL

The above case raises a critical question with regard to several recently published studies in which subjects received DBS in an effort to treat one illness, but instead saw serendipitous improvement in a comorbid psychiatric illness. One serendipitous discovery was reported by Kuhn et al. (2007) who attempted to treat a man with anxiety disorder by placing DBS electrodes into his nucleus accumbens, a major component in the reward circuit of the mammalian brain. While the patient's anxiety did not improve, he did see significant remission in his alcohol dependency, leading the group to propose the target as a potential treatment for alcoholism and addiction.

A second example comes from Hamani et al. (2008) who used DBS of the hypothalamus in an effort to help control a patient with morbid obesity. Although the patient continued to gain weight (a fact left out of the primary article and only included in the online supplemental materials) he did experience a flashback while receiving intra-operative test stimulation. This led the researchers to do a battery of studies to determine if stimulation to the same area at a lower level, which did not cause a flashback, could improve memory. To the surprise of the researchers, they found a significant increase in the subject's verbal memory. Based on this finding the authors proposed the anterior fornix (a structure adjacent to the hypothalamus) as a target for the treatment of dementia and began enrolling patients to study it further.

Finally, Israël et al. (2010) describes a case in which a woman was receiving DBS of the subgenual cingulate gyrus (Cg25) for treatment of depression. The authors noted that, although the patient continued to have relapses of major depression, she stopped experiencing symptoms related to a significant comorbid anorexia nervosa. Based on the remarkable improvement the patient experienced, despite her less remarkable improvement for her depression, the authors proposed Cg25 as a target for the treatment of anorexia nervosa.

There are several curious similarities among the cases above. First, the intended effect of DBS was either not seen or was not particularly robust. Second, the serendipitous effect on the comorbid illness (or enhancement of normal faculties in the case of anterior fornix stimulation for memory) was remarkable. Third, based on these cases all authors proposed that the stimulated sites be tested as targets for monotherapy for the responding illness. A final common feature was that at no point did the authors describe the patient receiving informed consent for the managing of the comorbid illness or for enhancing the patient's faculties (Earp et al., 2014), with DBS. The only paper that commented on informed consent was Hamani et al. which stated:

> The procedure was approved by the University Health Network Research Ethics Board, and written informed consent was obtained under the guidance of a hospital ethicist, who served as a consent monitor. The basis of the approval for this man was the refractory nature of the obesity, the exhaustion of reasonable therapeutic alternatives, and the possibility of reducing the health risks of chronic obesity should the intervention prove successful (Hamani et al., 2008).

In the passage above, the authors clearly stated a reasonable approach for obtaining informed consent for the treatment of the patient's obesity. However, they did not describe receiving the patient's consent for the use of DBS in order to enhance his verbal memory. Despite not reporting the patient's informed consent to have his memory augmented, they proceeded to run a battery of tests on the patient's memory function and, furthermore, did not mention discontinuing the treatment once it became apparent that DBS was not effective for the treatment of obesity.

The above cases raises a critical question: were these examples of "mind control"? The patients had unexpected alterations in their behavior and it appears, based on the descriptions of the cases, that the DBS was continued primarily because of these unexpected results. Further, the authors did not report that they repeated the informed consent process for the serendipitous alteration in the patient's behavior. The authors of this paper could conjecture that, once the researchers realized the unexpected effect DBS was having on their patient they consulted with him or her and received his or her blessing to continue therapy. Nonetheless, if they (or others) had not secured the consent of their patients for these new treatment indications, then they would be satisfying the *Result* (behavior change) *Consent* (happening without patient's consent) and *Intent* (behavioral change was the goal of DBS) criteria of mind control. Therefore, it is critical for clinicians and researchers to secure additional consent in the case of serendipitous therapeutic benefit in order to avoid the charge that they are committing an act of mind control.

CONCLUSION

We have argued that DBS is not synonymous with mind control; however, if not appropriately safeguarded, patients can be victims of mind control even without malice on the part of those controlling the stimulation, especially in the case of serendipitous treatment of co-morbid psychiatric illnesses. While many instances of mind control are easily identified, there are certain instances where the distinction is more ambiguous. This paper outlines a clear set of criteria to help more effectively and reliably clarify those ambiguous cases. For an act to be considered mind control it must alter the individual's behavior (*Result Criterion*) without his consent (*Consent Criterion*) and this alteration to the behavior of the individual must be the goal of the person or group controlling the alteration (*Intent Criterion*). Relying on the researchers' or clinicians' intuitions alone is not sufficient because those intuitions might easily become clouded such as in the serendipitous discovery of an effect of DBS. It is, therefore, important to note that in cases of serendipitous treatments of psychiatric illness patients also require the explicit consent for the treatment of the co-morbid illness, or else the case would qualify as mind control. It is the intention of the authors to minimize the risk of such accidents by clarifying the underlying concepts.

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Prostheses for the will

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INTRODUCTION: THE NEUROBIOLOGY OF THE WILL

The will is a complex set of cognitive (including affective and motivational) and motor capacities that enable us to initiate and complete action plans. Neurological and psychiatric disorders impair these capacities because of dysfunction in neural circuits mediating them. Parkinson's disease (PD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and other conditions can be understood as disorders of the will involving overactive, underactive or inactive critical nodes of these circuits (Lozano and Lipsman, 2013). Neural prostheses such as brain-computer interfaces (BCIs), hippocampal prostheses (HPs), and deep-brain stimulation (DBS) can bypass, replace, or modulate damaged or dysfunctional circuits and thereby restore or enhance the capacities necessary to translate intentions into actions. In this respect, they can be described as prostheses for the will.

Philosophers claim that for the will to be free, actions must not be generated by causal routes that bypass and undermine agent's control of the mental states that issue in them (Mele, 1995). Presumably, this would include manipulation of the brain by an artificial implanted device. Yet neural prostheses that bypass, replace, or modulate dysfunctional circuits do not undermine but instead restore this control when it has been lost and can enhance it when it is impaired by brain injury or neurodegeneration. They restore control of thought and behavior by restoring the relevant motor and mental functions. I will describe the different respects in which the three neural prostheses in question can achieve this goal.

BRAIN-COMPUTER INTERFACES: RESTORATION OF MOTOR FUNCTION

BCIs utilize operant conditioning and goal-directed thinking in restoring some degree of motor function. As motor prostheses, they can enable some individuals with paralysis caused by traumatic brain injury, neurodegenerative disease, or limb loss to move a cursor on a computer screen or a robotic arm by detecting signals in the motor cortex associated with intending to perform these actions. These systems may involve macroelectrodes placed on the scalp and connected to an EEG, electrodes implanted subdurally or epidurally, or a microelectrode array implanted in the motor cortex. What causes the cursor or robotic arm to move is the mental act of forming and executing an intention by the person manipulating the interface. BCIs may also enable those with disorders of consciousness or locked-in syndrome who retain a high level of cognitive functioning to reliably communicate their wishes about continuing or discontinuing life-sustaining treatment when they cannot communicate behaviorally. Difficulties with learning how to manipulate BCIs, sustaining attention to the task at hand, and the semantic capacity necessary to communicate for those with cognitive impairment are some of the challenges presented by this technology (Birbaumer et al., 2014). Whether a person using such a system can translate his or her thoughts into actions may depend on the extent of brain injury, which cortical circuits are intact, and how effective the practitioner is in training the patient to operate the interface. The extent to which the patient can do this successfully, and thus the extent to which he or she can exercise the motor component of the will, can be a matter of degree.

HIPPOCAMPAL PROSTHESES: RESTORATION OF MEMORY ENCODING

HPs to restore the cognitive function of memory have been used as prototypes in animal models but have not yet been used in humans. While they are at the developmental stage and may be ready for implantation in the human brain in the next 5 years, they remain a hypothetical intervention. Electrical stimulation of the fornix, which projects to a circuit consisting of the hippocampus and entorhinal cortex, improved semantic, working, and procedural memory in at least one person in a Phase I trial for early-stage Alzheimer's disease (Laxton et al., 2010). For those with this or other dementias whose hippocampal degeneration is too advanced to respond to neurostimulation, or for those with anterograde amnesia from traumatic injury to the hippocampal-entorhinal circuit, an HP replacing it might be able to restore the ability to encode new memories and learn and retain information (Berger et al., 2011; Hampson et al., 2013). It would do this by re-establishing inputs and outputs in this circuit. This structure is a component of the episodic memory system and one of the first structures to undergo cellular loss and tau pathology in Alzheimer's disease. Artificial reconstruction of neuron-to-neuron connections with a biomimetic microchip model replacing the hippocampal-entorhinal

circuit could improve and sustain semantic, working, and procedural memory in those with degeneration in brain regions mediating memory and enable them to continue performing cognitive and physical functions. Memory provides a cognitive basis on which to imagine counterfactual and possible courses of action in the present and future (Hassabis et al., 2007; Schacter and Addis, 2007). It thus plays a critical role in deliberation and decision-making. A prosthesis that could resolve anterograde amnesia by re-establishing the ability to encode, consolidate, and retrieve episodic memory could restore planning and decisional capacity and restore one component of the will.

Theoretically, it would not matter whether memory functions were maintained by a natural or artificial system, provided that the prosthesis connected in the right way with the neural inputs and outputs necessary for these functions. To a certain extent, memory retrieval is an involuntary process. We have some degree of control of this process insofar as we can make some episodic memories consciously accessible and use the information in working memory for immediate cognitive demands and in prospective memory to plan ahead. But memories that flooded our brains with information serving no such purpose could be a burden and an impediment to free action. Device makers and practitioners implanting and activating an HP would have to ensure that circuits mediating the encoding, consolidation and retrieval of episodic memory were neither underactive nor overactive. They would also have to ensure that the device integrated with adjacent circuits in the medial temporal lobes and did not interfere with nondeclarative memory systems such as striatum- and cerebellum-mediated procedural memory and amygdala- and brainstem-mediated emotional context memory. In addition, the encoding function of an HP would have to be compatible with the meaning the agent assigns to past events and memories of them. This meaning influences how the agent imagines future situations and forms action plans. Prostheses would not assign meaning to newly formed memories but would encode them with equal value-neutral weight. This could impair goal-directed behavior if it interfered with the person's capacity to select some past events as more valuable than others in deliberating about courses of action. The encoding of new memories by the prosthesis would have to complement meaningful long-term memories that already have been encoded and consolidated and are available for retrieval. So the HP would not only have to integrate with other circuits in the person's brain but also with his or her history as an agent with a past and future.

DEEP BRAIN STIMULATION: RESTORATION OF MOTOR AND COGNITIVE FUNCTIONS

DBS has the widest range of applications among neural prostheses, restoring or enhancing motor as well as cognitive functions. It can be used as both as a probe and modulator of activity in dysfunctional neural circuits implicated in neurological and psychiatric disorders (Lozano and Lipsman, 2013). DBS has confirmed the pathophysiology of PD as degeneration of dopaminergic structures in the nigro-striatal pathway of the basal ganglia. Unilateral or bilateral stimulation of the subthalamic nucleus (STN) or globus pallidus interna (GPi) have restored circuit integrity and resulted in significant improvement for many patients with PD and other movement disorders such as primary dystonia and essential tremor in their ability to perform voluntary bodily movements. While the technique is still experimental and investigational for psychiatric disorders, DBS has confirmed that dysfunction in brainstem dopaminergic structures such as the ventral tegmental area (VTA) associated with motivation and reward is implicated in depression with symptoms of anhedonia and avolition. Stimulation of the nucleus accumbens, which receives projections from the VTA, has resulted in relief of these symptoms in some patients whose depression had been resistant to pharmacological treatment (Schlaepfer et al., 2008). By restoring their capacity to consider and engage in pleasurable activities, DBS can restore one component of their will. In addition, because of its projections to frontal-striatal pathways mediating cognitive, affective, and motor functions, stimulation of the STN can modulate dysfunction in these pathways and release individuals with OCD from paralyzing obsessions and compulsions (Mallet et al., 2008).

The neuromodulating effects of DBS can re-establish and sustain optimal levels of neural function, preventing extremes of deficit and surfeit and promoting flexible behavior and adaptability to the environment. Overstimulating targeted circuits, or inadvertently stimulating the wrong circuits, in an attempt to release mental and physical constraints caused by one type of neuropathology could cause a different type and have an equally disabling effect on the will. In PD, for example, electrical stimulation of the STN or GPi can resolve hypodopaminergic activity causing motor, cognitive, and emotional inhibition. But imprecise stimulation or overstimulation of these brain regions may induce hyperdopaminergic activity and produce behavioral disinhibition and impulsive or addictive behavior (Castrioto et al., 2014). The ethical implications of altering brain circuits with this technique in terms of benefit and harm are evident in reports of Parkinson's patients experiencing both symptom relief and neurological and psychological sequelae (Muller and Christen, 2011; Christen et al., 2012). Motor and emotional effects of stimulating the STN or GPi can be difficult to dissociate because the basal ganglia include these motor nodes as well as limbic nodes. There is considerable overlap between them, with afferent inputs and efferent outputs regulated by the same neurotransmitter. Similarly, in MDD overstimulation of an underactive nucleus accumbens associated with anhedonia and avolition can cause hyperdopaminergic effects in the reward circuitry and result in pathological behavior in the form of euphoria, hypomania, and mania (Synofzik et al., 2012). The cost-benefit ratio of DBS for depression and other psychiatric disorders is still unclear. The increasing use of this and other brain-invasive technologies raises ethical questions because not all outcomes are positive. A recent study of DBS of the reward system for MDD showed promising results within a few days of stimulation at lower intensities. As in earlier studies, however, surgical risks such as intracerebral hemorrhage and psychiatric complications such as suicidal ideation and hypomania in some subjects, as well

as the high cost, were among the negative aspects of the technique (Schlaepfer et al., 2014). Some sequelae are not foreseeable, and it cannot be predicted which patients will experience them. This underscores the fact that this type of neuromodulation for psychiatric disorders remains experimental and investigational. Neural targets of DBS must be carefully selected and stimulation parameters adjusted in response to brain changes and neurological and psychiatric symptoms to maintain optimal levels of neural and mental function. Stimulation must sustain the neural and psychological mean between extremes.

Technological advances such as closed-loop feedback devices that can monitor and adjust to changes in the brain while circuits are stimulated can reduce the incidence of adverse effects. This would make them more tailored to individualized therapy in maximizing benefit and minimizing harm regarding the capacity to think and act. A recent study demonstrating positive outcomes from DBS at an early stage of PD suggests that it might have similar outcomes in treating psychiatric disorders if the effects on neural circuits are similar (Schuepbach et al., 2013). Electrical stimulation of dysfunctional circuits at an early stage of degeneration could strengthen synaptic connectivity, release trophic factors and possibly induce neurogenesis. This would be especially welcome in light of previous studies indicating that DBS for advanced neurodegenerative disorders can relieve symptoms but not alter the underlying pathology and disease progression. Even if DBS or other neural prostheses failed to arrest neurodegeneration, they might be able to delay or prevent further degeneration and enable patients affected by these disorders to retain some degree of control of their behavior by sustaining a certain level of cognitive and motor functions for longer periods.

CONCLUSION

The ability of DBS to modulate underactive and overactive circuits in neurological and psychiatric disorders can restore or enhance the physical and mental capacities composing the will. Although their range of applications is more limited, BCIs and HPs could bypass or replace dysfunctional pathways in cortical and subcortical areas mediating motor control and dysfunctional pathways in the medial temporal lobes mediating episodic memory. A BCI may restore the will to some degree by enabling individuals paralyzed from brain or spinal cord injuries to translate their thoughts into certain actions and communicate their wishes about medical treatment. An HP replacing a damaged hippocampal-entorhinal circuit might enable individuals to learn and retain information necessary for present cognitive tasks and future planning. These considerations about the neurobiological basis of the will and the effects of altering it show that there is much in common between neuroscience and philosophy and that each discipline can inform and be informed by the other. In different respects and in varying degrees, the three prostheses I have discussed can re-establish and sustain the structural and functional integrity of the brain circuits necessary for freely willed actions.

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How cognitive enhancement can change our duties

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This theoretical paper draws the scientific community's attention to how pharmacological cognitive enhancement may impact on society and law. Namely, if safe, reliable, and effective techniques to enhance mental performance are eventually developed, then this may under some circumstances impose *new duties* onto people in high-responsibility professions—e.g., surgeons or pilots—to use such substances to minimize risks of adverse outcomes or to increase the likelihood of good outcomes. By discussing this topic, we also hope to encourage scientists to bring their expertise to bear on this current public debate.

Keywords: cognitive enhancement, neuroenhancement, modafinil, methylphenidate, mental capacity, ethics, law, professional duties

INTRODUCTION

Whereas techniques for the augmentation of brain function are usually seen as beneficial when used as a form of medical treatment, both amongst the general public (Schelle et al., 2014) and in academia (e.g., Sandel, 2009) some concerns have been raised about the possible negative moral and social impacts of the use of these techniques in healthy people. For example, concerns about such so called "cognitive enhancement" include seeing it as a threat to the fairness and meaningfulness of competitive activities, or as a potential threat to a meaningful human life. Even though "cognitive enhancement" may refer to different brain intervention techniques like genetic modification, pharmacological substances, Transcranial Magnetic Stimulations (TMS), or Transcranial Direct Current Stimulation (tDCS; Bostrom and Sandberg, 2009), in this paper we focus on *pharmacological* cognitive enhancers such as methylphenidate and modafinil. These substances have been reported to modestly improve wakefulness, attention, concentration, learning and retention of memory, not only when taken by people diagnosed with mental deficits or disorders, but also when taken by healthy individuals (Repantis et al., 2010; Husain and Mehta, 2011; Coffman et al., 2014; Gilleena et al., 2014; Meinzer et al., 2014).

In what follows, we discuss a seldom-recognized but crucial way in which pharmacological cognitive enhancement may impact on our society's moral and legal norms: the availability of such enhancers might evoke *new duties* for certain people. In particular, it may impact on the *professional duties* of people engaged in jobs where the lives of other people are directly at risk (e.g., surgeons and pilots)—i.e., it may impact on what we can (legally) *demand* these professionals to do. By exploring this issue, we want to offer some insights into a particular way in which scientific work on brain function augmentation may impact on society: by enhancing our cognitive capacities, neuroscientific progress may change our duties to one another (for in-depth discussion see Vincent, 2011, 2013; Enck, 2014; Goold and Maslen, 2014; Santoni de Sio et al., 2014).

HOW PHARMACOLOGICAL COGNITIVE ENHANCEMENT CAN CREATE NEW DUTIES

Our main question may be framed in the following way: assuming that a certain kind of pharmacological enhancement proves to be relatively safe and effective at reducing risks of negative outcomes, may some people, in virtue of what is at stake in the performance of their professional roles (e.g., surgeons or pilots), be sometimes *legitimately expected* to cognitively enhance themselves even if they would rather not do so? Even though this question may sound counterintuitive at present, we think there are good reasons to assume that such an expectation might be a realistic scenario in the future. In particular, we think that the professional duty to use pharmacological enhancers may sooner or later be raised in tort cases at least under restricted circumstances, for instance in emergencies, when less invasive and at least as effective alternatives are not available. If this happens, judges will take a decision mainly through analogical reasoning. We thus think it is important to anticipate how such reasoning is likely to run. By having a clearer picture of such a possible future scenario, the scientific community and the public more generally will be able to think ahead about whether any pre-emptive steps need to be taken to forestall the development of foreseeable undesirable social, political, and legal consequences involved in such a scenario.

In the following we present three main points in support of our claim that a duty to enhance, as circumscribed above, may arise in the future.

Firstly, scientific and technological progress has already affected professional duties in the past. Surgeons, for instance, are nowadays expected to deploy many measures that enhance their performance and/or reduce the risks of fatal outcomes. Historically, this professional duty to take measures has gradually emerged over time, and progress in scientific and technological knowledge has been one decisive element in the creation of the duty. When, for instance, basic antiseptic procedures which are common today—e.g., cleansing hands with carbolic acid—were originally developed, their efficacy was not yet established, their risks for the user were unknown, they were available only in select research laboratories and medical practitioners were not expected to deploy them. But today, now that the clinical value of these techniques is widely recognized, and they are relatively inexpensive, largely free of risk, and ubiquitously available (Gawande, 2012), medical practitioners cannot legitimately reject the request to employ these techniques. The discovery of the antiseptic efficacy of carbolic acid, as it were, brought with it the creation of a duty to use it.

Of course, the analogy between cognitive enhancement medications and carbolic acid is far from perfect—while the former is highly invasive to an important domain, namely brain functioning, the latter is not even skin-deep. Therefore, one should not expect this analogy to be sufficient to make a case for the professional duty to use pharmacological enhancers. However, this analogy is arguably sufficient to make a more general point: when it comes to professions with a high societal value like those aimed at healing people or warranting their safety, it may be legitimate for society to demand professionals to not follow their individual preferences but rather the rules of good practice that are proven to lead to optimal results, including those requiring them to undertake particular treatments of their body. Even in the most democratic society, the value of individual freedom of choice of professionals is not protected unconditionally. For instance, at present we already expect medical or legal professionals to engage in continuing education programs. Often this is quite an invasion on people's lives since they must set aside time from an often already busy schedule to attend classes after hours, often losing sleep, and certainly losing personal time. But yet we do not think that this imposition on their freedom is an unreasonable one. We think that this is a sacrifice that we are entitled to expect professionals to make for the benefit of their patients and clients. The underlying thinking is that what's gained in terms of outcomes is presumed to be more important than the sacrifices that others have to make to secure those outcomes.

Secondly, it may certainly be insisted that things are different with pharmacological enhancers, and that no matter what happens with the compulsory use of non-invasive technologies or with compulsory non-pharmacological enhancement programs, the use of medical substances that directly affect the brain can never be imposed on professionals against their will. However, even as things currently stand we already sometimes expect some people to use medical substances that directly affect their brain for the benefit of others—namely, when we expect people who wish to operate motor vehicles but who are diagnosed with conditions like epilepsy and diabetes to take medical substances to prevent the negative effects of these conditions from adversely affecting others (*Knoxville Optical Supply, Inc. v Thomas*, 1993 WL 574 (TennCtApp Jan 04, 1993)). Naturally, a good reason for them to take these medications is simply the benefits to their own health. But it has to be noted that the argument which justifies legal coercion to use those substances in the case of the epileptic and diabetic motor vehicle drivers is not that the medical substances will benefit *them*—in a liberal democracy paternalism is rarely accepted as a valid justification for infringements on freedom—but rather that their not taking those medications would impose an unacceptable risk to *others* (if they should take to the roads un-medicated).

We offer the above example in support of two points. Firstly, there is already an existing and accepted practice of expecting one group of people to take brain-invasive medications for the benefit of other groups of people. Secondly, it makes little difference that these examples involve the use of medications to *treat* rather than to *enhance*, because the persons concerned are expected to take the medications not for their own benefit, but for the benefit of others. In fact, Queensland Health, the medical regulatory body of the North-East Australian state, has recently followed a similar reasoning pattern in relation to fatigue management. In their Queensland Health (2009), it is suggested that in order to cope with fatigue-related risks, surgeons could take up to "400 mg of caffeine [which is the] equivalent to about 5–6 cups of coffee" (78) because "[c]ompared with other psychoactive drugs (e.g., modafinil), caffeine is... more readily available and less expensive" (79). Given that the report explicitly cites modafinil, and that it only cites availability and cost as considerations that favor the use of caffeine over modafinil, we think it is perfectly conceivable that a future report may recommend such drugs to be used (cf. Maslen et al., in press). To be sure, one may still insist that this is not a desirable scenario, and that the protection of minds from external interference should be recognized as a human right. However, as a matter of fact, the right to "cognitive liberty" (Bublitz, 2013) is not (yet) protected by international human rights in the same way in which bodily integrity is, so that the scenario that we propose remains realistic.

Finally, one may wonder whether concerns about safety will in the end prevent the imposition of a duty to enhance in every situation imaginable. Admittedly, the long-terms possible negative effects of the use of cognitive enhancers are not sufficiently known (Madras et al., 2006; Volkow et al., 2009), and a greater scientific understanding of these substances is needed before normative conclusions can be confidently drawn (Maslen et al., 2014). However, it is also a fact that methylphenidate has been prescribed to children to treat the symptoms of attention deficit and hyperactivity disorder for well over two decades. We cite this example only to illustrate that there is at present already consensus about the relative safety of these drugs to prescribe them to the most vulnerable part of the population—namely, to children. This point is salient because if, as a society, we deem the costs or risks of particular cognitive enhancement technologies to be sufficiently low, then this may lead us, together with the other considerations

mentioned above, to impose a duty to use these medications onto some people at least in some emergency situations, namely when other more common forms of intervention like napping or being replaced by another worker who is not fatigued are not available.

A GLANCE INTO THE FUTURE

Admittedly, we are not (yet) in the scenario that we just described. The efficacy of pharmacological cognitive enhancement techniques in reducing the rate of fatal mistakes and thus enhancing the quality of performance of professionals like surgeons and airline pilots has not been established yet (Förstl, 2009; Repantis et al., 2010), and they are not even easily accessible. It is therefore not surprising that the law has not yet demanded any professionals to enhance themselves nor have lay people advanced such a demand.

As for the law, Goold and Maslen (2014) have offered a detailed legal analysis on the issue of whether surgeons who are at risk of making fatigue-related errors during patient care might be considered legally obliged to pharmacologically enhance themselves, i.e., if, at least under certain circumstances, there can be a *legal duty to enhance* for surgeons. Their conclusion is that, at the moment, such a legal duty *cannot* be imposed (at least in England and Wales). However, once one considers the reasons behind their conclusion, it becomes clear that Goold and Maslen's statement about the current legal situation is not necessarily incompatible with our claim about the future. Their case against the imposition of a legal duty to enhance on surgeons, in fact, critically depends on their reasonable doubts about the efficacy of current enhancers, and the possible negative side-effects of these substances. Moreover, this conclusion does not affect the validity of our theoretical point. In fact, as Goold and Maslen themselves explicitly state, in a *hypothetical* scenario in which efficacious and relatively safe cognitive enhancers were available, surgeons *might* be burdened with a duty to take pharmacological cognitive enhancers to reduce the risks of fatal fatigue-related error, at least under some emergency circumstances, namely when other, less invasive, options like napping or being replaced by another surgeons are not available. And it is *this* kind of hypothetical scenario that our reasoning has taken into account, and that future judges may have to decide upon.

As for lay people, they also seem to believe that no obligation to enhance should ever be imposed on professionals or other subjects (Maslen et al., in press). Many are indeed skeptical even about the moral *permissibility* of the use of pharmacological enhancers in any circumstance (Santoni de Sio et al., in press). Again, this is reasonable and understandable. Lay reasoning widely reflects the current state of affairs of scientific progress. From this perspective, lay reasoning is somehow similar to that of the above-mentioned legal scholars: because pharmacological cognitive enhancement is currently neither uncontroversially efficacious nor safe, people are legitimately wary and suspicious of it and reluctant to expect anyone to use it. However, lay reasoning may also reflect less rational and justified concerns. Medical enhancement substances are perceived negatively compared to other "natural" enhancers, and as a consequence the use of pharmacological cognitive enhancement might be stigmatized also in an irrational way (Faulmüller et al., 2013).

CONCLUSION

Reflections on the social impact of scientific and technological progress can come in different forms. On the one hand, we may reflect on how *current* technologies and techniques are already impacting on society. However, we may also wish to reflect on how the social, political, legal, and moral landscape may change due to pressure from reasonably expected *future* advances in science and technology, and think ahead about whether any pre-emptive steps need to be taken to forestall the development of foreseeable undesirable social, political, legal, and moral consequences. Adopting this latter "socially responsible innovation" approach (Moor, 2008; van den Hoven, 2013) which has recently been embraced also by the European Commission (2011), our paper has discussed the possible impact on society of future advances in pharmacological cognitive enhancement. We have argued that the availability of techniques that can enhance performance may in the future impose *new duties* on certain people under certain circumstances.

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Whose well-being? Common conceptions and misconceptions in the enhancement debate

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For this Research Topic on brain augmentation,[1] several authors discuss possibilities of brain stimulation (e.g., Duecker et al., 2014), pharmacology (e.g., Lynch et al., 2014), and psychobiological training (e.g., Chapman and Mudar, 2014). According to a definition proposed by ethicists, such procedures are human enhancement if and only if they are a "change in the biology or psychology of a person which increases the chances of leading a good life in the relevant set of circumstances" (Savulescu et al., 2011b, p. 7). Note how this definition describes the individual as malleable and the circumstances as given. The authors continue to explain that something counts as enhancement "so long as it tends to increase a person's well-being" (Savulescu et al., 2011b). Similarly, Nagel emphasizes the notions of happiness, well-being, and improvement in her discussion of the ethical challenges of enhancement and discusses the possibilities and risks related to neuro-technology and psychopharmacology (Nagel, 2014).

These and similar publications identify concepts like improvement or well-being as foundational issues of the enhancement debate. This raises important questions, such as who defines well-being and how to achieve it. In the three following sections, I will discuss the conceptualization of well-being, the framing of enhancement, and the translational promises given in the literature.

[1] http://www.frontiersin.org/Systems_Neuroscience/researchtopics/Augmentation_of_Brain_Function/1563

WHOSE WELL-BEING?

The majority of the experimental enhancement literature employs neuropsychological test designs developed to measure the presence of psychological impairment in terms of attention, learning, memory, and the like (for systematic reviews, see Repantis et al., 2010; Smith and Farah, 2011; Bagot and Kaminer, 2014). Referring to this literature in the human enhancement debate is problematic: That these tests can be used to inform clinical decisions does not warrant their usefulness outside the clinics. Higher test scores do not necessarily reflect a happier, more meaningful life in general. Yet, clinical studies are often cited in ethical discussions to debate the benefits and prospects of enhancement for the healthy. This carries the risk of a normative fallacy, namely, the identification of clinical benefit with overall well-being.

This risk is often accompanied by another one, namely, that of a localizational fallacy. It consists in only targeting individuals psychobiologically, not their circumstances. In contrast, established measures such as the *World Happiness Report* which are provided by United Nations institutions measure well-being macroscopically: GDP per capita, social support, healthy life expectancy at birth, freedom to make life choices, generosity, and perceptions of corruption together explain 75.5% of the international variance of happiness rankings in 2012 (Helliwell et al., 2013). It goes without saying that these indices are also based on norms, but not primarily driven by clinical needs, instead broader in scope, and developed by institutions which are representing people at large at least remotely.

An advanced recent proposal consists in the *OECD Guidelines on Measuring Subjective Well-being*, operationalizing subjective well-being as consisting of life satisfaction, affect, and eudaimonic well-being, which in turn consist of three subcategories each, namely, income, health, and work satisfaction; anger, worry, and happiness; competence, autonomy, and meaning and purpose (OECD, 2013). Based on these guidelines, people can create their own *Better Life Index*, prioritizing 11 pre-defined dimensions (such as housing, jobs, education, or safety), and more than 60,000 citizens from OECD countries have so far participated[2]. Using such methods, the risk of a normative fallacy can be minimized, since people can choose their own standards, although ideally they should be able to design the methods, too. The results, including meaningful differences between countries, indicate that human enhancement need not be localized in individual psychobiology, but can also be achieved by socio-political reform.

It turned out, for example, that safety is valued most highly by participants from Japan, income and housing by those in the United States, and education by those in Finland. To assess the relevance of brain stimulation, pharmacology, and psychobiological training for human enhancement,

[2] http://www.oecdbetterlifeindex.org (accessed May 30, 2014)

it would be informative to know to what extent these methods can contribute to human well-being broadly understood. If it turned out that the causal link is very remote and speculative, proponents of human enhancement could conclude that socio-political reform is more promising a means than individual psychobiological intervention. In the terms of the definition proposed by Savulescu and colleagues above, this amounts to not changing the subject with respect to the circumstances, but the circumstances with respect to the subject.

FRAMING AND RELEVANCE

Cognitive enhancement has been framed as common by leading scholars in the field who described it as a means "not to get high, but to get higher grades, to provide an edge over their fellow students or to increase in some measurable way their capacity for learning" (Greely et al., 2008, p. 702). Greely and colleagues subsequently stated that almost 7% of students in the US already use stimulants like amphetamine or methylphenidate for cognitive enhancement, with the prevalence reaching 25% on some campuses. In a comment gathering some anecdotal evidence, I pointed out that such framings occur regularly in the ethical literature (Schleim, 2010). This impression is shared by Lucke et al. (2011) who also carried out a media analysis of newspaper articles and found that 94% of the reports mentioning the prevalence of psychopharmacological enhancement described it as common, increasing, or both (Partridge et al., 2011). Actually, 66% of these reports referred to the academic literature as evidence. It goes without saying that this framing of the practice as common and/or increasing lends the topic high urgency.

In the systematic review of prevalence studies in student samples by Smith and Farah, the most comprehensive I know of, the authors conclude that "[a]mong college students, estimates of use vary widely but, taken together, suggest that the practice is commonplace" (Smith and Farah, 2011, p. 717). Referring to this review, Nagel even claims that the usage is increasing (Nagel, 2014). Both claims are difficult to justify, though, with respect to cognitive enhancement: First of all, it is in the eye of the beholder what to count as common. The decision is complicated by the variance in findings, ranging from 1.7 to 34% in studies with more than thousand students ($N = 12$; mean = 9.5%, median = 6.7%). Sometimes the reported figures reflect past month prevalence ($N = 2$; mean = 4.6), sometimes they refer to last year ($N = 6$; mean = 6.7) or even lifetime usage ($N = 4$; mean = 16.1). Secondly, their authors often investigated non-medical use, which allows many different motives for stimulant consumption that do not indicate cognitive enhancement, such as feeling high or losing weight. Smith and Farah summarize that in those surveys addressing motives, study-related answers were dominant but regularly accompanied by recreational/lifestyle choices (Smith and Farah, 2011). However, detailed interviews with consumers at an elite university in the United States suggest that emotional rather than cognitive motives drive non-medical use even for improving studying, since people report feeling better and overcoming motivational problems with stimulants (Vrecko, 2013).

For the time being, framing the relevance as common and non-medical use as cognitive enhancement is therefore, in my view, in contrast to the best available evidence. It is even more problematic to claim that the practice is increasing, because this would require repeated cross-sectional studies of comparable samples under standardized conditions. Yet, even within research groups definitions of inclusion criteria and ways of sampling data often differ. Nevertheless, what has been increasing steeply during the last decades was the production of stimulants like amphetamine and methylphenidate, particularly in the United States, and publications on enhancement (see **Figure 1**). That the former increase is not reflected in the prevalence studies previously mentioned is most likely due to the concept of non-medical use. Both drugs are controlled prescription stimulants and most epidemiologists as well as ethicists strictly distinguish medical use as treatment from non-medical use as either drug abuse or enhancement.

This framing has wider ramifications for the scientific community: Without the treatment/enhancement distinction, the consumption of stimulants can and has been analyzed by medical sociologists under labels such as medicalization or pharmaceuticalization (Abraham, 2010; Bell and Figert, 2012); and without the claim that enhancement is common or even increasing, the problem appears much less urgent. By framing stimulant consumption as enhancement and common, though, neuroethicists generated a new ethical problem, new prospects and risks, that they subsequently could manage (see also Conrad and De Vries, 2011; Littlefield and Johnson, 2012). Indeed, the steep increase in publications on enhancement topics coincides with the inception of instutionalized neuroethics (Marcus, 2002; Farah, 2012; **Figure 1**). It thus becomes apparent that both, medical sociologists and neuroethicists, have a conflict of interest in framing stimulant consumption in the competition for research funds and high-impact publications.

PROMISES

The abundant literature on enhancement suggests the possibility to increase learning, to feel better, and to become more intelligent by means of brain stimulation, pharmacology, or psychobiological learning (Savulescu et al., 2011a; Farah, 2012; Hildt and Franke, 2013; Nagel, 2014). However, it is also noted that there is much that is not known about the working of stimulants, for example, and that funding of empirical research is difficult because it is not about treatment and therefore outside the purview of disease-oriented schemes and it is too applied for funders of basic science (Smith and Farah, 2011). As mentioned in the section on well-being above, it is furthermore not clear what the goal of the intervention is and whether changing the individual in its circumstances is actually more promising than changing the circumstances for the individual.

However, by analogy with biological psychiatry it is possible to at least engage in informed speculation on what the situation might be like had there been more agreement on the research goals and more funding of enhancement research. When psychiatric researchers started to prepare the fifth edition of the *Diagnostics and Statistical Manual of Mental Disorders* (DSM) they set the aim to include biomarkers, particularly based

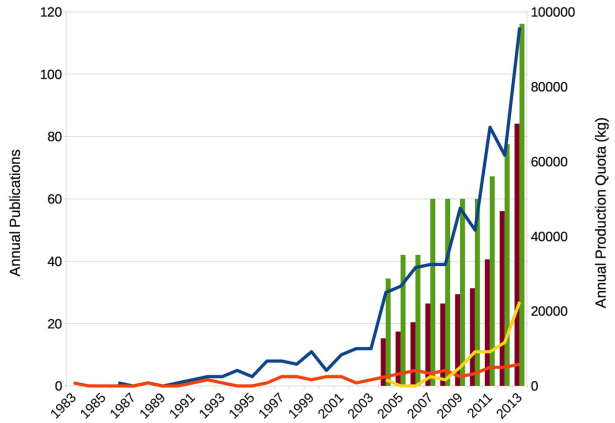

FIGURE 1 | Stimulant production and enhancement papers increased strongly. Lines show a steep increase in publications on cognitive enhancement (blue) and neuroenhancement (yellow), but only modestly on mood enhancement (orange). Publication numbers are based on a Web of Science topic search. Bars show a strong increase in production quotas for amphetamine (red) and methylphenidate (green). In the shown 10-year period from 2004 to 2013, the former increased 5.5-fold, the latter 3.4-fold, after quotas had already been increasing in the 1990s (not shown, but see Rasmussen, 2008). Figures based on US Drug Enforcement Agency, October 2, 2013, http://www.deadiversion.usdoj.gov/quotas/quota_history.pdf (accessed May 30, 2014), accumulating amphetamine produced for sale and conversion.

on genetic and neuroimaging research, to improve diagnosis and treatment (Hyman, 2007). Note that the previous fourth edition of the DSM listed more than 300 disorders and their respective symptoms guiding clinical diagnosis (APA, 2000). It is now widely acknowledged that this attempt for the fifth edition was unsuccessful, though views on why this happened and what to do about it differ (Hyman, 2010; Kapur et al., 2012; Walter, 2013; Kirmayer and Crafa, 2014). Certainly, with more than one billion dollars annually spent on research at the National Institutes of Mental Health alone, lack of funding was not the problem[3]. In the light of decisions by pharmaceutical companies to close their psychiatric laboratories because of negative prospects (Amara et al., 2011; Van Gerven and Cohen, 2011) and reports that prescription stimulants do not even seem to have a lasting positive effect on individuals diagnosed with Attention Deficit/Hyperactivity Disorder (Currie et al., 2013; Sharpe, 2014), the frequently promised translational possibilities of enhancement research may be unrealistic (Schleim, 2014). Perhaps we need to minimize risks of committing a translational fallacy, too.

When Quednow speaks of a "phantom debate" (Quednow, 2010) or Lucke and colleagues want to deflate the "neuroenhancement bubble" (Lucke et al., 2011), they appear to have good reasons for doing so. We should also not forget that people in many countries are already quite happy and that in those where they are not, the difference in happiness is probably not due to limited access to enhancement technology. Clinical research for those suffering from a disorder should keep the priority over enhancement. It could even be the case that too much focus on increasing well-being and happiness, on how things might yet be better than they presently are, might make more people unhappy in the first place; or, in Schopenhauer's words:

"We then recognize that the best, which the world has to offer, is a painless, calm, bearable existence and we confine our claims to these in order to accomplish them better. Because not to become very unhappy, it is the best means that one may not demand to be very happy." (Schopenhauer, 1874, p. 434; author's translation).

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[3]http://www.nimh.nih.gov/about/budget/index.shtml (accessed May 30, 2014)

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Cognitive enhancement kept within contexts: neuroethics and informed public policy

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Neurothics has far greater responsibilities than merely noting potential human enhancements arriving from novel brain-centered biotechnologies and tracking their implications for ethics and civic life. Neuroethics must utilize the best cognitive and neuroscientific knowledge to shape incisive discussions about what could possibly count as enhancement in the first place, and what should count as genuinely "cognitive" enhancement. Where cognitive processing and the mental life is concerned, the lived context of psychological performance is paramount. Starting with an enhancement to the mental abilities of an individual, only performances on real-world exercises can determine what has actually been cognitively improved. And what can concretely counts as some specific sort of cognitive improvement is largely determined by the classificatory frameworks of cultures, not brain scans or laboratory experiments. Additionally, where the public must ultimately evaluate and judge the worthiness of individual performance enhancements, we mustn't presume that public approval towards enhancers will somehow automatically arrive without due regard to civic ideals such as the common good or social justice. In the absence of any nuanced appreciation for the control which performance contexts and public contexts exert over what "cognitive" enhancements could actually be, enthusiastic promoters of cognitive enhancement can all too easily depict safe and effective brain modifications as surely good for us and for society. These enthusiasts are not unaware of oft-heard observations about serious hurdles for reliable enhancement from neurophysiological modifications. Yet those observations are far more common than penetrating investigations into the implications to those hurdles for a sound public understanding of cognitive enhancement, and a wise policy review over cognitive enhancement. We offer some crucial recommendations for undertaking such investigations, so that cognitive enhancers that truly deserve public approval can be better identified.

Keywords: ethics, neuroethics, cognitive science, neuroscience, cognitive enhancement, culture, public policy

In its disciplinary stance and practice, neuroethics acknowledges the most sufficiently confirmed theories of the neural and cognitive sciences as (provisionally) accurate in an overriding manner. Indeed, neuroethics should not ignore or set aside such theories if/when these prove to be inconvenient for, or incompatible with, practical applications, principled values, private intuitions, or popular common sense. Nor should these theories be muted when neuroethical engagement of real-world issues, questions and problems are needed. The actual functions of the brain, as best as can be described at present, is—and must remain—fundamental to any and all neuroethical discourse and deliberations.

In light of this, we argue that neuroethical inquiries into cognitive enhancement should establish the crucial role for context, especially socio-cultural contexts to conceptions of the "cognitive", so as to better define the realities of neuroethical debates about cognitive performance enhancement (and enhancers). We write in support of investigations into putative neuro-enhancers which adopt the theoretical stance that hoped-for improvements cannot be evaluated in isolation from human activities that provide the meaningful context to any alteration in performance. At key points of our argument we appeal to empirical studies examining performance alterations, to exemplify our concern for due attentiveness to real-world situational conduct as possible enhancers are tested and utilized. Where relevant contexts to neuroscientific inquiry and information utilized for normative purposes are taken seriously, the work of formulating and guiding neuroethical quandaries would be appreciably strengthened.

With our argument for this role of context established, we then outline crucial policy considerations regarding neuro-cognitive enhancement, and raise some warnings about over-eager advocacy for enhancement. While remaining cautiously optimistic toward opportunities for cognitive enhancement, we insist upon fostering public understanding of the issues, and upon development of sound public policy. In this way we join the ranks of other neuroethicists who have voiced similar views and concerns (Illes and Bird, 2006; Levy, 2011; Farah, 2012; Gunson, 2012; Fitz et al., 2014; Maslen et al., 2014b; Racine et al., 2014).

As a discipline and set of practices, neuroethics must utilize the best cognitive and neuroscientific knowledge to shape incisive discussions about what could possibly count as enhancement in the first place, and what should count as genuinely "cognitive" enhancement. Where cognitive processing and mental life is concerned, the lived context of psychological performance is paramount. In the absence of any nuanced appreciation for the control which performance contexts and public contexts exert over what "cognitive" enhancement could actually be, enthusiastic promoters of cognitive enhancement can all too easily depict brain modifications as being good for individuals and for society. Such claims are not unaware of serious hurdles—hurdles noted in oft-heard observations and express concerns—that may impede enhancement derived from neurophysiological modifications. Yet those observations are far more common than penetrating investigations into the implications that such hurdles may evoke—both for the sound public understanding of cognitive enhancement, and for wisely informing policy to guide and govern cognitive enhancement. To wit, we offer what we maintain to be crucial recommendations for undertaking such investigations, so as to better identify cognitive enhancers that truly deserve public approval and policy support.

Civics and general ethics can be idealistic, but neuroethics should not be unrealistic, and must be liberated from ethical theorizing done in ignorance of the most contemporary understanding of the structure and function of the brain. In this way, neuroethics must strive to comprehend the genuine basis of conceptions of self, society, and morality, and rely on changes or replacements to those conceptions when and where scientifically warranted (Shook and Giordano, 2014).

ENHANCEMENT STANDARDS

Bioethicist Thomas Murray identifies two primary meanings to the term "enhancement": first, "to advance, augment, elevate, heighten, increase"; and second, "to increase the worth or value of." (Murray, 2007) In both definitions, context is axiomatic. Numerous scholars have similarly noted the "metric" and "normative" dimensions of this term. For an organism such as a human being, enhancement implies opportunities to improve capacities or abilities—features that can be simultaneously measurable and valuable, and possibly moral, as well. Structure and function cooperate and even interfuse, even as they have distinct implications for ethicality, and this can confuse discussions of enhancement, in general, and of "cognitive enhancement" more specifically.

Hence, it is important to ask whether a particular modification is responsible for altered performance of a specified task. If it is, then that physiological modification is a *performance modifier*, and if that change is regarded as positive relative to some normative standard, then we can refer to it as a *performance improver*. Furthermore, if we call a particular activity an "intellectual" task, then we are really talking about an *intellectual enhancement* for performing that task. This physiological modification may be labeled as an "intellectual enhancement" in an easy, colloquial manner of speaking, although at this point in the description, a scientific understanding of the brain or intellectual capacities is not yet involved.

In light of that science, however, it can no longer be enough to simply track cognitive functions and the resulting performance on particular tasks to verify enhancers. An alteration to a physiological process associated with cognition can be measured and compared against some organic standard. Has enhancement occurred? It is still too soon to say; a pre-set physiological standard is never simply a "given" normative standard. Detecting a physiological alteration within an individual requires an individual-relative standard against which to measure that alteration, to be sure. But what may be expected from one person needn't expected from others. Setting someone's neurological functioning as the standard for any human brain's "normal" functioning, so that a baseline for cognitive functioning can be established in preparation for detecting cognitive improvement done to anyone, is quite another normative decision. One that normality standard is put in place, then actual cognitive function (for the processing and integration of various types of sensations, memories, emotions, subconscious valuations, and so on) can be estimated and compared against some standard of normality. Even after this has been done, it still may be premature to say whether or not the evoked changes represent an enhancement; reliable cognitive performance (for one's overall management of life activities and achievements) must be judged in light of some *ethical* standard. Just as human-normal performance can't be reduced to any single individual's functioning, ethically responsible enhancement cannot be reduced to any superiority over what has been conventionally set as generically normal for "average" humans.

Standards at the three levels of individual physiology, human-generic normality, and sensible ethicality all compete for prominence where definitions of "enhancement" are concerned. Furthermore, it doesn't help that the complexities of the nervous system can permit odd scenarios in which an increase in physiological function(s) might diminish cognitive ability; and diminishing a specific type of cognitive function might be conducive to optimizing a person's actions or general well-being (Earp et al., 2014). Rigidly demanding only one standard, or one direction by that standard, with which to dictate enhancement is a stubborn path to take, and one that we assert any rational approach to neuroethical analysis and discourse should avoid.

Letting the concept or term "enhancement" stand for any non-therapeutic benefits conferred by an intervention is a common way to avoid taking any (if not all three) standards seriously. Does enhancement begin when a medical treatment exceeds the usual dosage or typical extent of repair? Perhaps enhancement refers to those instances where treatment yields physiological functioning

beyond the normal range. Or, enhancement might entail evoking superior performance that lends distinct advantages to life. Arguing over these options overlooks the mistake that enhancement can begin where therapy ends. It is a mistake that is easy to make.

Therapeutic medicine simplifies its standards because it takes all of humanity to be its proper field of work; a good treatment for a health deficiency generically helps any patient suffering from that problem. So long as the reference class remains "humanity," then a physiological "average" functioning can be equated with generic normality, and there would only be "disease treatments" (aiming towards normality) and "enhancement treatments" (aiming beyond normality). However, patients aren't so generic in the real world. Broad culture and local society are contexts that always exert influence.

For example, what can count as normality and abnormality within a particular culture might not obtain for all of humanity too. But, if that culture's influence (viz.—power) is sufficiently strong, clinicians, patients, publics and governing bodies might not necessarily notice, or care (or feel empowered to act even if they did). Furthermore, any social group within that culture could come to regard itself as the proper reference class, expressly if that group enjoys some status and/or privilege. When that social group requests medical treatment, it is set in terms of what counts as "group normal" rather than just "culturally normal" or "normal for humanity." For example, when middle-aged privileged men take their reference class as "adult men like us", they surely aren't thinking about "all human males on the planet between the ages of 18 and 80." Nor are they taking their reference class to be people very much like them, such as "successful men between 45 and 65." Instead, what counts as "normality" is the reference class that these men desire to be, perhaps something like "healthy guys in their 30s-50s." So, in effect they want what counts as "subgroup optimal." Growing approval among a subgroup about using a drug or device off-label lends credence towards that intervention's status as an "enhancer", even if that subgroup expects more than just intellectual performance (Hildt et al., 2014; Wade et al., 2014). Interventions can transition from enhancers back to treatments, as well. If a culture's medicine proves willing, then treatment for achieving subgroup optimality could be labeled as medical "therapy", rather than enhancement.

Neuroethics must take close notice of: (1) the kinds of standards applied for determining enhancement; (2) the chosen reference class serving as the background against which enhancement would stand out; and (3) the selection of "normality" or "optimality" as the envisioned goal to enhancement. Medicine's traditional focus on generic remedies for universal application to all humanity is not the best (or perhaps even a viable) framework for identifying and classifying enhancements. Cultural inheritance, group socialization, personal values, and physiological factors are each and all necessarily involved when defining and addressing enhancement. The advent of "personalized" medicine aiming towards the individualization of diagnostics and treatments should raise awareness across neuroethics that specifics will matter to ever greater degrees in the future.

ENHANCING COGNITION IN CONTEXT

The temptation to regard cognition as an entirely neurophysiological matter, amenable to objective study, definition, and measurement, isn't just a symptom of overreaching reductionism or scientism. Frustration with too much context can set in for anyone reconciled to cognition's reliance on brain functioning. If cognition is, in some sense, objectively present as subjects undergo experimental study, then it could be objectively modified. Researchers would be able to determine when and how cognition is improved when compared against some preset standard of cognitive ability. Serious attention to cognitive enhancement came to the fore as a consequence of experimental facilitation of cognitive ability, with due caution leveraged against exaggerated claims of capability, meaning and utility. (Metzinger and Hildt, 2011; Sahakian and Morein-Zamir, 2011; Sandberg, 2011; Chatterjee, 2013; Cohen Kadosh, 2013; Hildt and Franke, 2013). Hard lessons learned from pharmaceutical studies apply to any sort of performance effects produced by alteration of brain structure and function (Luber, 2014).

Neuroethical attention must be paid to wider contexts of neurological manipulation, beyond the fairly objective and narrow ways that cognitive performances can be adjusted in desired directions. Determining if a neurological intervention can actually produce a desired enhancement is one thing; ascertaining that some sort of adjustment is truly cognitive (in the expected manner) is quite another, and these distinctions deserve priority. Imitating medicine's quest for therapies that have universal utility for anyone suffering from a generic health problem is no longer a wise undertaking for the application of 21st century biomedical advancements. As well, we maintain that it is equally unwise to promote enhancements as if they could be universally beneficial for generic cognitive improvements to anyone's intellectual performances. Indeed, we argue that there may not be such a thing as a "generic enhancement to cognitive performance." A major reason for this involves cultural contexts. Two people from two different cultures, or even two people from two subgroups of the same culture, may not necessarily agree on what is cognitively adjusted by some alteration of neurological function. Thus, neuroethical inquiry cannot avoid an interpretative circle: some group of people ascribe a "function" to a cognitive process in service of a task that is considered to be "normal"—but this is a social imposition of normality on a neurophysiological process. In this way, performance, not neurophysiology in isolation, decides functionality, and what counts as "normal".

For illustration, consider an analogy: suppose a practical way to increase muscle mass (without deleterious side effects) is offered as a general "athletic enhancer" that could be used by anyone. Athleticism depends on one's musculature, surely, so given this rationalization, more muscle should enable more athleticism. But muscle mass alone does not equate with athletic ability (or in some cases even potential ability!) For example, one can take anabolic-androgenic steroids (AAS) to augment muscle mass. As matter of fact, these very likely will lend something of an "edge" to (important) dispositions and characteristics necessary for improved athletic performance (i.e.,—muscle size and

strength; Llewellyn, 2010). However, the underlying premise is that the agent is increasing specific qualities of muscle (e.g.,—diameter of muscle fibers, contractile force, etc.) that have been shown to be operative in a number of athletic events.

Herein though, are important caveats. While an AAS may yield mass and strength gains, these are only preparatory for "training effects", because an athlete must still train for a particular sport. AAS can facilitate that training, but if training is conducted improperly, less success at a sport is a likely result. Furthermore, different physiological agents can elicit distinct effects. Some will enable gains in muscle mass but not necessarily facilitate definition; others will be more lipolytic, and produce lean, muscular density, but will not greatly increase mass, and so forth. Also, AAS does little for aerobic endurance *per se*, just as an endurance-facilitating agent (such as erythropoietin, EPO) does little for mass or strength. (consult Llewellyn, 2010). The adage is: The right agent for the right effect.

These points account for the ample evidence—and practical wisdom—indicating that if one wants to become proficient in a particular sport, then it is necessary to vigorously train in that sport. There are generic athletic training exercises, but each sport must evaluate their utility. For example, cross training can lend overall benefits to components of athleticism, but it doesn't necessarily permit direct performance gains peculiar to each sport. Only after specific kinds of athletic performances, and the individual athletes performing them, are identified and targeted, would an intervention be intelligently developed and employed to exert positive effect(s) within selected contexts. Expanding upon this example of sports performance, we may expect that most types of neurological interventions intended for the enhancement of performances displaying much complexity may only work best in conjunction with cognitive training regimens. Not only must any trials confirming a modification for cognitive improvement involve successful routine practice under controlled conditions, only implementing that modification in conjunction with strenuous performance training result in the practical enhancements to performances actually valued outside of any laboratory.

More generally, it is naïve to suppose that a compensatory adjustment, much less an enhancing adjustment, could be generically assigned validity across all of humanity. Even best-case scenarios must remain stubbornly diffuse. Calling a performance test a "cognitive performance test" and observing that individuals who are subjected to intervention "x" perform better doesn't mean that some purely cognitive functioning has been isolated and targeted as the improved factor. Fortunately, careful research is hardly so naïve, as recent exemplars have noted (Pringle et al., 2013). The lesson is that no one pondering cognitive enhancement should assume that higher cognition can occur in some "pure" forms, no matter how specific the task. To begin with, multiple affective and motor processes are interfused with the functional components that are operative in executive control. In turn, executive control is interfused with every sophisticated practice acquired during childhood and adolescence. This is especially the case when dealing with higher cognition manifesting in social and moral behaviors (Shook, 2012; Specker et al., 2014).

Enculturalization takes advantage of advanced executive control for instilling specialized task performances, such as learning mathematics and logic. It is no paradox that the more cognitively abstract the task, the more it has a cultural rather than a purely biological basis; hence such tasks are very much subject to the vagaries of cultural history and practice. Something as simple as conceptualizing number and amount has been shown to be culturally variant (Núñez, 2011). Similarly, memory performance has been shown to be culture-dependent and -influenced (Gutchess et al., 2011; Hewer and Roberts, 2012). Cultures contribute to cognition as much as cognition contributes to culture (Han and Pöppel, 2011; Ishii, 2013; Kim and Sasaki, 2014). Even context is contextual as far as cognition is concerned, since the developing sensitivity towards, and responsiveness to, environing interpersonal context displays cultural variability (Imada et al., 2013).

The contextual factors raised here are not posed to endorse a thorough relativism or dismissive eliminativism about potential enhancers. Cognitive enhancement can be quite real, when and where it is created. To be sure, confirmable cognitive enhancements can be achieved because improved cognitive (i.e.,—intellectual and/or emotional) performances by selected and trained participants can be measured under controlled conditions. Generally speaking, under sufficiently similar conditions, similarly altered people having enough in common will perform similarly, all other things being equal. What more could be expected from science?

ENHANCEMENT IN PUBLIC CONTEXTS

Desires to "improve the human condition" conjure proposals for a proverbial "rising tide" of neuroscientific and neurotechnological modifications that will "raise all boats"—and brains. But when realistically looking ahead, unavoidable questions loom: How much can humans be enhanced without deforming or destroying aspects of the social or natural world on which life relies? and, Will human character and moral progress be sustained if hopes for enhancement become realized? Some have supported a duty to urge enhancers and even intervene with required enhancement, once we can apply a safe and effective intervention. However, our comprehension of long-term consequences is limited, and encouraging (what may be long-lasting) modifications without ensuring equally durable individual welfare is reckless (Rossi et al., 2013).

Shall the position of the responsible individual prevail instead? Letting individuals choose for themselves is no less reckless. Even when individual benefits can be guaranteed, it must be asked: who should receive them? The answer, "All who can benefit," is no answer at all, because it will not be the case that everyone will have the same, or even similar, access at the same time. Differential access is inevitable in a world of finite time and resources. Such differential access is *prima facie* unjust, as those who already possess certain traits, attributes, and/or resources will likely and quickly get even more. Hence, essential concerns for distributive justice arise from the position of society at large. The distribution of improved health and lifestyle status, and even improved moral status, will always be a social concern (Buchanan, 2011; Douglas, 2013).

Worries over distribution cannot—nor should not—be easily dispelled. Those with the least assets are those most unlikely to get access to state-of-the-art scientific and technological interventions. It is unrealistic to assume that some massive shift in the social architectonics of medical resource allocation will occur so as to allow neuroscience and neurotechnology to close the gap between those who "have" and those who "have not." Given this reality, does everyone really want a society where the people getting the most enhancement(s) are precisely those enjoying great wealth? The prospect of cognitive enhancement surely highlights this worry: intelligence does what character directs, and the kinds of characters getting so wealthy in a society may not be the people to be trusted with even more intelligence—and power. Proponents of unlimited access to enhancement simply point the way toward an unbalanced distributive scheme. Contests between rival distribution methods can be debated in ethics, but they get adjudicated in politics.

Hence, entering the realm of politics becomes unavoidable. The politics surrounding access to enhancement will be intense. Of equal importance is the temptation to use brain science within agendas of political power to control fundamentally biological aspects of individuals' and communities' existence (invoking what Foucault referred to as biopolitics; see Foucault, 2008; Anderson et al., 2012). Bioethical and neuroethical analyses cannot avoid addressing science as a public good; ethics as a search for the good and the right; and politics as the participation of citizens in decisions about the guidance of public order. As public debate over the impact(s) of enhancement interventions accelerates, the search for principled guidelines has ensued, and neuroethics has become ever more involved (Bostrom and Sandberg, 2009).

Irrespective of whether enhancement is regarded as a bountiful cornucopia or a ticking bomb, the differing contexts of enhancement radically transform its biopolitical status. Recall from a previous section our attention to the choice among physiology, normality, and ethical standards for identifying what counts as enhancement. Experimental medical research focusing upon physiological alterations (typically) emphasizes interventions for those who are the most unhealthy. Policy tends to approve funding for basic research if and when it could soon help those with the most severe, and/or epidemiologically extensive, health conditions. These prioritizations wouldn't work in the realm of enhancement for three reasons. First, a traditional approach to funding and engaging research would tend to leave most enhancements on the theoretical drawing board. Second, while there may be desires for expensive advanced research into fundamental neurological mechanisms that can be targeted for cognitive performance enhancement, unless these approaches can be ascribed to incur some "therapeutic" benefit against an identified disease, disorder or (medical) condition, financial and administrative support for broad scale research and translation of outcomes and products would tend to be lacking. Third, while there may be a viable—and perhaps growing—market for certain cognitive performance enhancements, it is difficult to generate the funding necessary to support and sustain exploratory research required for translation to safe commercial technologies (unless developed and marketed as "non-medical" products such as toys and games, which then raises the specter of inapt and/or unsound development, distribution and use; see, for example, Giordano and DuRousseau, 2011; and Plischke et al., 2011).

A related issue is the contemporary medical endorsement of interventions that restore or sustain "normality." Explicitly and implicitly this position conforms to socio-cultural requirements that all people should seek and exhibit "normal" functioning, rather than (what is regarded to be) abnormal or anti-social conduct that deviates from socially established standards. What posture should be assumed when (a) certain people seek optimal functioning in pursuit of what they personally deem as the apex of the good life, and/or (b) society sets requirements that individuals in special roles (such as physicians, pilots, peace officers, or warfighters) must attain some level of optimal functioning? (Giordano et al., 2013; Goold and Maslen, 2014) Medicine's laudable work in service of living a good life isn't automatically extendable to living a great life, or to achieving great performance in a socially-sanctioned service. Justifications for specialized enhancements for enabling idiosyncratic lifestyles or for extraordinary public service will not necessarily be obtained in and from medical principles.

A second set of examples arise from our earlier discussion of the cultural relativism inherent to the precise identification of cognitive improvements. Medicine's due caution with clinical application, watching carefully for deleterious health and lifestyle side-effects, relies upon cultural consensus about what constitutes "normal" performance in daily life (Gini et al., 2010). Those seeking significant enhancements, by contrast, won't be interested in conforming to cultural norms about ordinary performance, and medicine may not be able to restrain them. When the recipient of an enhancement is achieving extraordinary performance levels and feeling empowered to transgress cultural expectations in the name of greatness (despite the risks), what social institution or cultural tradition can and will reign-in their pursuits?

Evidently, society turns to law for such proscriptions. Yet, here it becomes necessary to ask how restrictions of, and prohibitions against certain types and extents of enhancement will be determined. Targeting concrete neurological modifications for legal bans (i.e.,—imitating medical bans of performance enhancing substances for professional athletes, and/or scheduling certain drugs) has the merit of objective verification. But this only spurs those seeking improved types of cognitive performance to find alternative physiological methods not yet banned or detectable, and the chase is begun anew.

POLICY PRIORITIES AND THE ROLE OF NEUROETHICS

Frustration over excessive contextualization is a perennial complaint. Simplifying matters can seem attractive when modest advances require prompt address and short-term priorities are within reach. Simplification would be possible if the construct and term "enhancement" satisfied defined and pragmatic scientific and ethical criteria. That way, any continued debate would be centered on those improvements that were already deemed to be fairly good for people in general, so far as could be scientifically and ethically determined. Warnings are certainly in order that current enhancement interventions rarely prove to be wholly effective

or without deleterious effects. Unsurprisingly, wide agreement among scientific, ethics, and policy communities can be found on the view that enhancing interventions shouldn't be counter-productive or harmful to overall health.

However, we posit that practical risk-benefit analyses aren't entirely sufficient. Detailed ethical scrutiny is required before any such practical improvements can be classified as good enhancers. It is wise to demand that putatively enhancing interventions do not diminish self-control or autonomy, degrade personal growth or self-worth, or diminish life-management and social skills (de Melo-Martín, 2010; Allhoff et al., 2011). These demands can be reasonably placed upon envisioned enhancements, even if they aren't applied so stringently to proven medical therapies. Improvements towards health are usually consistent with personal empowerment, and the consequences of restoring normal functioning are largely understood. By contrast, the longer term effects of experimental enhancements, especially cognitive performance enhancements, on the psychological self and internal self-conceptions and motivations are among the least predictable and understood aspects of this issue. Ethics is rightly concerned about the vital capacities for autonomy, dignity, and morality. All the same, as we have noted, setting high standards for cognitive performance enhancing interventions need not cast dark suspicions upon the persistent search for, and studies of enhancements. A number of scholars have advocated for practical and ethical standards while endorsing the pursuit of enhancement (including Buchanan, 2011; Glannon, 2011; Giordano, 2012; Heinrichs, 2012; Clark, 2014; Maslen et al., 2014a). In short, the goal is to develop helpful interventions able to meet these high standards.

If such normative thresholds are maintained, public and regulatory approval could be a helpfully expedited matter. But approval may not be automatic. Labeling an intervention as an "enhancement" once it makes individual lives demonstrably better can't be the final hurdle before regulatory approval (Giordano and DuRousseau, 2011). One further—and arguably major factor—that cannot be omitted is the wider public context. We believe that this is where the broadest and deepest deliberations over the wisdom of enhancement should occur. We are forced to ponder what shall be done when sound public priorities cannot automatically approve genuinely ethical enhancements.

Policy principles should be well informed, ethical, and just. When some reliable enhancements are deemed safe and effective, and seem capable of promoting the good life, why wouldn't they be approved through policy and law? Here, it is important to appreciate that sincere advocacy of genuine individual enhancers could still be under-informed, potentially unethical, and possibly unjust. In those cases, public wisdom should lean against approval.

In this regard, two issues must remain distinct: First, it must be asked, and determined, if an intervention is a genuine enhancer. Second, if it is, then it must be asked if this enhancer is something that sound policy can approve and sanction. The criteria by which an enhancement is deemed conducive for the "good life" cannot be the same criteria that are used to determine whether to approve it. In the open space of public deliberation, it must be possible that sound policy can proscribe or prevent something that is presently understood to be reliably conducive to the "good life".

Here we avoid assumptions that knowing what is conducive to the good life for each person constitutes knowing what is ethical and wise. We also avoid the position that knowledge about what is conducive to the "good life" for everyone constitutes knowing what is ethical and wise. Rather, we posit an alternative stance. We argue that (1) well-informed policy would use more information than just the scientific facts about a performance enhancer promoting the "good life"; (2) ethical policy would use other ethical criteria beside simple promotion of the "good life" (individually or collectively); and (3) just policy may prefer a stable and well-ordered society that isn't advancing the individual or collective "good life" quite as fast as could be technologically possible (or imagined by technophiles).

Gazing upon the stance we propose, eager advocates of enhancement might ask why objective scientific facts couldn't or shouldn't lead the way, especially when cognitive performance enhancement seems so modest, practical, and generically useful? In doing so, they appear to endorse the general ethical guideline that:

> *A sound policy decision will always approve what, in light of ascertainable scientific facts, can be expected to be an enhancement to an individual that is conducive to what "our society" regards as the "good life."*

This guideline does not represent our position; we deem it unwise and replete with confusions, and when it appears to be doing the real work behind hasty encouragements of cognitive performance enhancement, we deplore it. Whether this is the actual view of any bioethicist or neuroethicist, or just a caricature for academic target practice, we cannot really say, because few scholars have explicated their meta-ethical presumptions. We do assert, however, that this stance is inadequate to meet the urgent complexities and contextualities inherent to authentic human life as we all must actually live it. In fact, there is little that is genuinely neuroethical in it. Our call for a neuroethics that takes context seriously, especially where cognitive performance enhancement is the issue, isn't merely fodder for academic debate.

Sarewitz and Karas (2012) outline several different approaches that can be adopted in order to make choices and decisions about cognitive enhancing technologies. Among those, our view aligns with the "optimistic" approach, via engagement of a managed technological optimism that best represents our position as relevant to ethical decision-making processes and public policies in this field. We endorse continued research into cognitive performance enhancements. We also call for the need to optimize definitions of any/all concepts and terms, and to equally define the contexts in which any cognitive task optimization can/would occur. Only from that point can one be optimistic that a progressive, non-static concept of the human and human function will be realistically entertained and enhanced, both practically and ethically. This position takes a pluralistic, democratic approach towards options of emergent (rather than merely proscriptive) governance, and the final section of this essay points to ways that neuroethics can play a supportive role.

We posit that a contextualized neuroethical outlook allows for better-informed approaches, utilizing all relevant interdisciplinary input, for considering what therapies and enhancements

could be. It permits neuroethical deliberation to rise above local conventionality and a single social ethos, to instead survey the rich cultural diversity of human self-understandings and dynamic cognitive capacities. And, it encourages neuroethics to render verdicts against destabilizing and unjust procedures in policy debates that rashly extend medical models beyond their proper functioning.

This neuroethics isn't proscriptive, nor does it seek to uniformly obstruct enhancement. In its naturalistic basis, it establishes grounds to view the human as engaging biology (through intellectual and physical tools) to optimize survival and flourishing in changing ecologies. And in its appreciation for the human as a bio-psychosocial organism it engenders an interdisciplinary approach (conjoining anthropology, sociology, economics, and political science) to depict and address ethical issues within the contexts in which human activities are conducted. Thus, in the spirit of cognitive enhancement itself, neuroethics as a discipline—and in its methods, approaches, and practices—should embody and enable greater human self-understanding, and improve our public deliberations over the many dimensions of life that we treasure.

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Cognitive biases can affect moral intuitions about cognitive enhancement

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Research into cognitive biases that impair human judgment has mostly been applied to the area of economic decision-making. Ethical decision-making has been comparatively neglected. Since ethical decisions often involve very high individual as well as collective stakes, analyzing how cognitive biases affect them can be expected to yield important results. In this theoretical article, we consider the ethical debate about cognitive enhancement (CE) and suggest a number of cognitive biases that are likely to affect moral intuitions and judgments about CE: status quo bias, loss aversion, risk aversion, omission bias, scope insensitivity, nature bias, and optimistic bias. We find that there are more well-documented biases that are likely to cause irrational aversion to CE than biases in the opposite direction. This suggests that common attitudes about CE are predominantly negatively biased. Within this new perspective, we hope that subsequent research will be able to elaborate this hypothesis and develop effective de-biasing techniques that can help increase the rationality of the public CE debate and thus improve our ethical decision-making.

Keywords: cognitive enhancement, rationality, cognitive bias, attitudes, de-biasing, moral intuitions, brain function augmentation

COGNITIVE ENHANCEMENT AND BIASED REASONING

The enhancement of cognitive brain functions by means of technology has become a reality. Recent research has demonstrated that various pharmaceuticals can have—at least modest—performance-enhancing effects in healthy individuals (for reviews, see Repantis et al., 2010; Husain and Mehta, 2011). In line with these findings, the off-label use of pharmacological substances like methylphenidate (e.g., Ritalin-®) or modafinil (e.g., Provigil-®) seems to be prevalent, in particular among students (Herman-Stahl et al., 2007; Smith and Farah, 2011; Dietz et al., 2013), and professionals in very responsible jobs like physicians (Franke et al., 2013). It has even been argued that the use of such substances might become an implicit requirement for individuals in certain professions (e.g., Maslen et al., in press). Non-pharmacological methods of cognitive enhancement (CE), such as gene therapy or neural implants, could become more widely used in the future (Bostrom and Sandberg, 2009). Even though there is considerable use of CE, recent research shows that the general public has strongly negative attitudes regarding the introduction and use of CE (for a review, see Schelle et al., 2014).

In this article, we argue that these concerns are partly driven by pervasive cognitive biases. A bias is a systematic deviation from a standard of rationality (Baron, 2005), an error frequently committed by the human mind. We use the definition of "rationality" common in cognitive science, referring to normative models of accurate belief formation (Foley, 1987; Audi, 2001) and optimal decision-making in order to achieve one's goal (Dawes, 1998). (Ir)rationality is therefore relative to the goal of having accurate beliefs or to goals in general. Thus, while some cognitive patterns may be suboptimal with regard to a particular goal, they may be perfectly optimal with regard to another. For illustration, consider "status quo bias", which we will address in the following section. If, upon reflection, an agent consciously and stably places some intrinsic value on the status quo, then in no sense can the agent be said to irrationally prefer the status quo (i.e., to make a cognitive mistake in doing so). However, the available evidence suggests that human agents do not, upon reflection, intrinsically care about the status quo, or at least to a significantly lesser degree than their immediate intuitions would have it: the experiments documenting our intuitive status quo preference (e.g., Samuelson and Zeckhauser, 1988) are interesting because they reveal a fact about our intuitive decision-making which our reflection disapproves of and is thus irrational. Also, nearly all action-guiding moral theories have an account of when the status quo should be modified, which is why the general bias towards it will tend to bring about suboptimal moral outcomes (c.f. Bostrom and Ord, 2006). Furthermore, if by "moral" decision-making we mean decision-making that is optimal from an "altruist" or "impartial" perspective, then

non-related goals such as status quo preservation will lead to irrationality, too. Hence, it is justifiable to classify the status quo bias and the other biases we are discussing below as, indeed, biases.

The aim of this paper is to offer a new perspective on the debate about CE by identifying cognitive biases that affect our common intuitions and moral reactions. We will first give a rough overview of the academic debate and the public's view of CE and then discuss a number of potential biases that are likely to influence widespread judgments about CE.

In the academic debate about CE, opinions of critics (often bioconservatives) and supporters (often transhumanists) are quite sharply divided. Critics often question its medical safety, considering the potential side effects and unknown long-term health risks (Healey and Rayner, 2008). Critics also see CE as a threat to human autonomy (Habermas, 2003), authenticity (Elliott, 2004) humility and solidarity (Sandel, 2004) and equality and fairness (Fukuyama, 2004). Proponents, on the other hand, focus on the potential positive aspects and potentials of CE. For instance, Savulescu (2006) points out that the introduction of CE could help decrease unfair natural differences in abilities. Bostrom (2008) emphasizes the enormous positive leverage effect that CE could generate in the future. He speculates that a 1% increase in all scientists' cognitive performance "would amount to an indirect contribution equal to 100,000 times what the average scientist contributes" (p. 2). Others note that CE is not relevantly different from traditional forms of enhancement, such as information technology (Harris, 2010).

Recent research reviewing the general public's attitudes towards CE has shown that lay people share many of the critics' concerns about CE (Schelle et al., 2014). Participants from samples of students or parents, for example, fear that safety is not ensured (Forlini and Racine, 2012; Partridge et al., 2013). They think that CE could lead to peer pressure and thus undermine our autonomous decisions (Forlini and Racine, 2009). Also, they worry that unequal distribution of CE would result in an unfair advantage of a privileged few (Fitz et al., 2013). These views are often reflected in exaggerated reports by the media and might even lead to severe aversive social consequences for users (Faulmüller et al., 2013). The Guardian, for example, has described CE substances as "capitalism's wonder-pills", which "turn you into the closest human approximation there is to a machine" (Mahdawi, 2012).

We believe that the common concerns about CE are justified at least to some extent, and a greater scientific understanding of CE is required in order to draw confident conclusions (Maslen et al., 2014). Most importantly, long-term safety of CE is not currently ensured (c.f. Husain and Mehta, 2011) and is being called into question (e.g., Urban and Gao, 2014). Nevertheless, we speculate that the public's views on CE are negatively biased. While the involved biases do not necessarily undermine any specific argument for or against CE—these would need to be evaluated on their philosophical and scientific merits—they might partially explain the general opposition to CE as well as the selective focus on certain arguments and exaggeration of their relative weight. It is not unusual for human cognition to selectively search for certain classes of arguments and systematically neglect or undervalue certain others (c.f. Kunda, 1990 on "motivated reasoning")—a bias that might affect the judgments of both opponents and proponents of CE. Biases may lead people to come up with a set of arguments that expresses sound considerations but is significantly incomplete or weighted wrongly. We thus propose that in order to fully explain prevalent opposition to CE, it is necessary to look into the role biases play in the CE context. Awareness of these biases is a precondition of rational public debate about CE, which in turn is needed for developing and establishing optimal social and legal regulations.

Empirical research into biases over the last four decades has shown that human reasoning is very prone to systematic irrational patterns, i.e., cognitive biases (e.g., Tversky and Kahneman, 1974), especially when the subject matter is as complex, novel, abstract and ideologically loaded as is the use and regulation of CE (Cosmides and Tooby, 1992; Kahan et al., 2013). We argue that a number of cognitive biases well-documented in psychology and behavioral economics partly explain prevalent negative attitudes towards CE. While we believe that attitudes towards CE are predominantly negatively biased, there may also be biases leading us to irrationally favor CE. We will indicate some biases likely to affect judgments about CE and illustrate why and how they may be impairing our judgments in this context. Thus, our aim is to suggest several hypotheses about potential irrational sources of the prevalent (negative or positive) attitudes towards CE. Some of the biases on our below list have been studied in behavioral economics, such as status quo bias, loss aversion, risk aversion, scope insensitivity. The others—omission bias, nature bias, and optimistic bias—have been addressed more in psychology and philosophy. Our application of the knowledge about biases to the CE debate is comparatively novel, as is the application to ethical issues in general. We hope to offer a valuable perspective as a contribution to more rational public debate on controversial ethical issues involving new practices or technologies. Since ethical questions often involve high stakes, this endeavor can be expected to yield important results for public ethical debate.

POTENTIAL COGNITIVE BIASES

STATUS QUO BIAS

Status quo bias describes the tendency to prefer the current state of affairs over a change even if a change would result in better expected outcomes. For instance, Samuelson and Zeckhauser (1988) presented participants with hypothetical choice tasks about financial investment, which either were defined with a clear status quo or not. Participants were significantly more likely to choose the option designated as the status quo compared to the same option that was not labeled the status quo. Numerous further experiments reliably demonstrate this effect (e.g., Kahneman et al., 1991). It seems plausible that popular aversion to CE is partly due to status quo bias: it may partly result from the pure fact that CE constitutes a novelty. Historically, new ideas and technologies have often encountered strong aversion and opposition at first (Jay, 1981; Weil and Rosen, 1995), but became accepted at a later point in time. Coffee—a traditional form of CE—provides an instructive example: it was first considered an unacceptable drug and even forbidden in some countries (Weinberg and Bealer, 2001; Cowan, 2005). Bostrom and Ord (2006) have already drawn

attention to the role status quo bias likely plays in the debate about CE. They also suggest a de-biasing tool—the *Reversal Test*—designed to expose and overcome status quo bias. If we believe that the enhancement of certain cognitive abilities will have negative consequences, we should consider the reverse: if an increase in intelligence is judged as negative, would a decrease in intelligence be judged favorable? If not, we are committed to claiming that our current level of intelligence is at an at least local optimum. This is, of course, possible but would require further justification. Obviously, it is an empirical question whether the introduction of CE actually results in net positive consequences or not. In case it would, however, status quo bias still exerts a psychological force against its endorsement. Empirical research can potentially expose the prevalence of status quo bias by, for example, observing whether people come to a different conclusion after reflecting on the rationale of the Reversal Test and applying it to the context of CE.

LOSS AVERSION

Loss aversion describes the tendency to weigh losses more than gains (Kahneman and Tversky, 1984). In monetary contexts, for example, loss aversion results in a stronger dissatisfaction after losing $1 than satisfaction after gaining $1 (Kahneman and Tversky, 1984). Whether something is perceived as a loss or as a gain depends on how the decisional situation is framed: one can either "get a $1 discount" or "avoid a $1 surcharge". Loss aversion can act on its own, but may also be a source of status quo bias (Bostrom and Ord, 2006). Maybe we recognize positive as well as negative consequences that the introduction of CE likely entails, such as the potential benefits due to enhanced intelligence on the one hand and the fear of increased unfairness in society due to unequal access to CE on the other hand (Fitz et al., 2013). But due to loss aversion, we likely tend to exaggerate the weight of the negative consequences relative to the positive ones.

RISK AVERSION

Risk aversion describes the tendency to undervalue an option that is less certain compared to a more certain option with equal expected outcome value (Kahneman and Tversky, 1984). Since preserving the status quo usually involves less uncertainty than a change does, risk aversion may be a further source of status quo bias, and it can act on its own as well. Consider a gamble where you have the option A of winning $1000 with a chance of 85% or the option B of winning $800 for sure. Most people prefer option B to A. However, option A has a higher expected value of 0.85 * $1000 = $850 and is therefore the rational decision if one values money linearly. As we are constantly faced with uncertainty, we are in fact dealing with such gambles all the time. We may be reluctant to introduce CE simply because its expected consequences involve probabilities that deviate more strongly from 100% and 0% than do the ones of the status quo. For example, methylphenidate almost certainly improves memory (for a meta-analysis, see Repantis et al., 2010), but there is a chance of long-term adverse effects (King et al., 2006). Though the expected utility calculation may favor the use of methylphenidate in certain cases, people are likely to retain a preference against it due to risk aversion and a resulting "precautionary principle" heuristic.

OMISSION BIAS

Omission bias describes the tendency to judge decisions differently depending on whether the same outcome is brought about through an act or an omission (Spranca et al., 1991). More specifically, people consider harms that have been caused by action worse than equal harms caused by omission. Ritov and Baron (1990) observed that parents often show reluctance to vaccinate their children. The expected harm of non-prevented disease is much greater than the expected harm of vaccination (Gangarosa et al., 1998), but parents seem to overvalue the expected harm caused by the vaccination because it is the result of their action. Similarly, we may fear that the introduction of CE is likely to or may cause harm. However, CE may also prevent harms from occurring and thus refraining from introducing may be a harmful omission, i.e., a missed opportunity for reducing harm. Due to our general omission bias, we are likely to systematically overvalue the harm of introducing CE compared to the harm resulting from not introducing it. For example, people might believe that the use of CE substances by medical doctors potentially causes active harm by inducing sleep disorders (Partridge et al., 2013)—but they might neglect or underestimate the potential positive consequences of doctors' increased ability to focus, i.e., the potential negative consequences of inaction. Rejecting CE may lead to greater harms suffered by more people overall. This question cannot be settled by unreflective intuition but requires open—un-biased—scientific investigation.

SCOPE INSENSITIVITY

Scope insensitivity occurs when people don't assign appropriate weight to the quantity of a decisional option (Kahneman, 2000; Desvousges et al., 2010). For example, a study has demonstrated that people are willing to pay the same amount of money to either help 9,000 people or 90,000 people who are at risk (Kahneman and Knetsch, 1992; Baron and Greene, 1996). This is irrational if one's goal is to help people and have everyone count the same, for the money one is willing to pay should then scale linearly with the number of people affected. It seems that our ability to intuitively represent such large numbers and their relations correctly is quite limited. In the context of CE, a probable implication is that we are not giving appropriate weight to the enormously high number of individual decisions, people (and generations) potentially affected by the consequences of introducing CE and thus to the importance and priority of the CE issue.

NATURE BIAS

Several studies on peoples' attitudes towards CE have revealed that natural CE substances are seen as less harmful and less ethically problematic than artificial ones (e.g., Bergström and Lynöe, 2008). For example, in a study with university students, participants were more likely to consider the use of artificial CE substances morally wrong than herbal ones (Scheske and Schnall, 2012). These judgments seem to be impaired by a form of nature bias (c.f. the fallacy of *appealing to nature*), i.e., a tendency to view the "natural" as good and the "unnatural" as bad. Given

that many examples of "natural and bad" (e.g., diseases) as well as "unnatural and good" (e.g., medicine) things exist, it is highly questionable whether tracking the "natural" tracks what people (would) actually assign value to, and it is clear that it is not intrinsically morally relevant according to the "altruistically/impartially optimal decision-making" criterion.

OPTIMISTIC BIAS

Some biases may also be pushing people towards an overly optimistic evaluation of the consequences of introducing CE. An example is the optimistic bias described by Chapin and Coleman (2009), which causes people to underestimate the possibility of negative outcomes. Examples include people underestimating the risk of becoming a victim of crime, of losing money in the markets, or of getting lung cancer after smoking (Weinstein and Klein, 1996). In the context of CE, people might underestimate the dangers, such as negative side effects, that CE could entail.

An additional source of optimistically skewed views of CE might result from biased reduction of cognitive dissonance by people who are already using forms of CE. When confronted with falsificatory information about CE, such as documented health concerns, users might experience discomfort—cognitive dissonance—and be likely to selectively adopt beliefs that justify their behavior (Festinger, 1957).

Thus, there are potential biases leading to an overly positive attitude towards CE. Overall, however, it seems there are more well-documented highly prevalent biases likely to cause irrational aversion to CE than biases in the opposite direction.

CONCLUSION

We have aimed to offer and motivate the perspective that biases are likely to impair judgments about CE, mostly in the negative direction. We are aware that the above list of biases is incomplete and speculative and hope that empirical research will further elaborate on our suggestions. It must be emphasized that "biases" often do provide sensible decisional rules of thumb—after all, many of them seem to have proven to be successful heuristics for our evolutionary ancestors. However, the practical scope of this argument is very limited first because our current environment is different from our evolutionary environment, and second because the metaphorical goals of our genes that have been served by some "bias-heuristics" need not coincide with our goals (Stanovich, 2004). Nevertheless, the existence of such biases cannot alone undermine the soundness of any objection to CE. But they can explain why people, including policy makers, may take an unreflective or one-sided position on such debates. More generally, many of our moral intuitions about controversial practices are likely to be influenced by such cognitive biases. Not only do we require psychological interventions such as remedial heuristics, we require good ethical argument and relevant scientific evidence to identify which of our moral intuitions are justified, and which are not.

We believe the CE debate would benefit from research investigating the role cognitive biases play in judgments about CE and from the subsequent development of techniques that help people judge the relevant issues in a less biased way. These techniques should be simple heuristics (Larrick, 2004) that are easily applicable in the context of CE. Bostrom and Ord (2006) *Reversal Test* or Savulescu (2007) *Loss/Gain Heuristic* are examples of such heuristics. Psychological research could test whether people's attitudes towards CE change after applying de-biasing techniques, i.e., by being made aware of the biases potentially impairing their judgments. If they do change, we have reason to assume that cognitive biases play a role in the current attitudes towards CE.

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The role of expectations, hype and ethics in neuroimaging and neuromodulation futures

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The production of *expectations* or future-goals for the development of techniques which "read" and modulate brain function, represent an important practical tool for neuroscientists. These visions-of-the-future assist scientists by providing focus for both individual and cross-disciplinary research programs; they encourage the development of new industrial sectors, are used to justify the allocation of government resources and funding, and via the media can help capture the imagination and support of the public. However, such expectations need to be tempered by reality. Over-hyping brain imaging and modulation will lead to disappointment; disappointment that in turn can undermine its potential. Similarly, if neuroscientists focus their attention narrowly on *the science* without concomitant consideration of its future ethical, legal and social implications, then their expectations may remain unrealized. To develop these arguments herein we introduce the theoretical concept of expectations and the practical consequences of expectations. We contextualize these reflections by referring to brain imaging and modulation studies on deception, which encompass the measurement-suppression-augmentation range.

Keywords: expectations, hype, ethics, brain modulation, neuroimaging, deception

INTRODUCING EXPECTATIONS

On May 25th in 1961 during a special address to Congress, a young and charismatic US President J.F. Kennedy presented an incredibly exciting prospect to Congress and the entire nation: a manned moon landing. He was asking Congress to share his vision, and in so doing to invest an astronomical budget in research and development to increase the likelihood of that vision becoming reality. Less than a decade later that vision was achieved with the Apollo 11 mission and the first moon walk: "one small step for man, one giant leap for mankind" (Neil Armstrong, 1969). Kennedy was perfectly aware that the required technology was not yet available in 1961 but he was well informed about its potential and knew a thing or two about the power of expectations.

Proclaiming the start of the Decade of the Brain on 1st January 1990, President Bush senior stated "The cooperation between [...] agencies and the multidisciplinary efforts of thousands of scientists and health care professionals provide powerful evidence of our nation's determination to conquer brain disease". He raised public awareness and brought to the fore a series of targets (e.g., stopping or curing Alzheimer's disease), which have not been quite met yet but the attention and investments brought upon relevant neuroscientific research see us at a clear advantage compared to our colleagues trying to meet the same targets 25 years ago.

When discussing scientific and technological advancement the concept of *expectations* adopts the shape of; goals, promises, visions of a future reality, "wishful enactments of desired futures" (Tutton, 2011, p. 413), and "real-time representations of future technological situations and capabilities" (Borup et al., 2006, p. 286). The value of such expectations, as a powerful precursor to future scientific and technological advances, cannot be underestimated as both a conceptual and a practical tool.

In this paper we begin by setting out the benefits to neuroscientists of employing *expectations*. This positive message is then balanced by a discussion of *hype* and its potential negative connotations for research programs. We finish by positing that if neuroscientists temper their expectations of future scientific and technological advances with social, ethical, and legal concerns, they will be better placed to avoid the drawbacks associated with hype while maintaining their ability to enjoy the benefits expectations can bring.

EXPECTATIONS: CONCEPTUAL AND PRACTICAL BENEFITS

On a conceptual level, expectations (as described above) represent *the potential pre-manifestation* or *genesis* of a future scientific or technical advance which has yet to be attained. To illustrate; neuroscientists envision a future whereby neuroimaging and brain stimulation techniques have been developed which, say, detect deception and/or increase the disposition and the ability to lie

and deceive (Karim et al., 2010; Mameli et al., 2010; Karton and Bachmann, 2011), "simply and safely influenc[e] the human will and freedom by interfering with deception" (Priori et al., 2008, p. 455; see also the "deception inhibitor": Bohning et al., 2004). They may also envision military applications whereby the ability of human operators to sense and assess threats in the real world is enhanced by noninvasive brain stimulation (e.g., Parasuraman and Galster, 2013). These particular near-to-medium term expectations are typically based on converging evidence from a small series of original precursor studies on human participants conducted in one or more laboratories around the world. When neuroscientists envision a future whereby in-helmet ultrasound transducers could be used to remotely control brain activity (Tyler, 2010; Sato et al., 2014), or where a time-slowing pill may be used in law enforcement and prisoner incarceration (Heaven, 2012; Anderson, 2014), or "brain prostheses" can be used by the military to enhance memory for complex environments or existing memories can be wiped out from the brain of personnel under capture (Moreno, 2012) they are envisioning medium-to-long term expectations. Here the know-how needed to achieve these particular goals remains largely unavailable and it is claimed that the ethical and legal implications of such enterprise are still relatively imponderable (Attiah and Farah, 2014).

What makes these particular expectations of specific interest to neuroscientists is that through a combination of their training, expertise, accumulated knowledge, and access to funding and specific equipment, neuroscientists find themselves well placed to successfully act and bring these expectations and visions into reality. This is not to claim that they are the *only scientists* capable of fulfilling these expectations; merely that they may enjoy a head start on their competitors when attempting to do so.

Moving beyond the conceptual, it is via its practical benefits that the true power of expectations becomes recognizable; for expectations possess the power to assist turning future-visions into tangible advancements. With similarities to the concept of the *self-fulfilling prophecy* (see Merton, 1948), future expectations have been described as possessing performative or generative powers (Borup et al., 2006) in that they are "crucial to providing the dynamism and momentum upon which so many ventures in science and technology depend" (Brown and Michael, 2003, p. 3). By studying past advancements, it has been recognized that expectations can provide the following benefits (see: van Lente, 1993; Hedgecoe and Martin, 2003; Borup et al., 2006; Konrad, 2006; Pollock and Williams, 2010; Bakker et al., 2012):

- A focal point to guide and drive research activities, as well as a common vision/bridge with which to enhance interdisciplinary interactions and communication.
- A promise of future benefits with which to justify and legitimize the mobilization and allocation of financial resources and other forms of support.
- The means of attracting the attention and engagement of diverse actors and potential collaborators; from scientists to investors, governments, NGOs and policy actors.
- They enable the production of experiments, models, research projects, and calculations.
- The construction of future scenarios for shaping a technology, as well as the formation of a consensus or structure to counterbalance the inherent uncertainty over the potential of a new technology which is highest during the early development stages.
- A means of enlisting public support through the presentation of possible future(s).

Within the life sciences expectations of future medical advancements have repeatedly been employed by specific research areas seeking to benefit from the points listed above. These expectations have included; the promise of lives being saved and the development of new cures for diseases as the result of human embryonic stem cell research (Rubin, 2008); the development of anti-aging treatments which will extend human lives (Mykytyn, 2010); and the expectation that by identifying one's genetic makeup, pharmacogenetics will deliver bespoke, personalized medications (Limdi and Veenstra, 2010).

Within neuroscience, and in particular the study of neuroimaging and brain stimulation, we can readily identify how neuroscientists are employing expectations in their efforts to secure supporters and resources for research, attract collaborators and potential customers for spin-off businesses, and provide focal points with which to guide research. All of this is achieved through the presentation of possible futures where brain imaging and modulation advances have been successfully developed. What follows is a brief description of some of these research programs, accompanied by the envisioned advances (the expectations) they are predicted to produce. While presenting these, we will intentionally embrace such expectations (whether or not we believe they are realistic), as this will help making the points we are raising in the following sections even more obvious.

EXPECTATIONS ABOUT THE FUTURE OF BRAIN IMAGING AND MODULATION: THE CASE OF DECEPTION

Riding a wave of exciting technical developments in neuroimaging, one popular research enterprise that has provided fertile ground for boosting expectations on a global scale is the study of deception. Here deception is defined as the concealment of the truth, which often takes the form of a memory, in order to mislead. On average humans are thought to be badly equipped to detect deception when the person attempting to deceive is unfamiliar to the observer (Bond and DePaulo, 2006). Expectations in this area have included a promise of a future whereby the scientific detection of deceptive claims and behaviors would add a game-changing weapon to the arsenal of forensic sciences, police, the judiciary, and military and security agencies worldwide. Whether that can be ever achieved is still open to speculation.

Historically a multitude of deception detection systems have been invented and employed by public and private bodies with variable success. Few such systems survived in the present; and none has been scientifically proven to solve the deception detection problem in the real world. The most popular system so far

has arguably been the polygraph, however, on close inspection, it was deemed unreliable; though since its myth is very hard to debunk, it still has use as a deterrent (NRC (National Research Council), 2003; see also Moreno, 2012). More recently, advances in functional Magnetic Resonance Imaging (fMRI) and neural decoding techniques prompted expectations that mind-reading (or more accurately brain-reading; Gazzaniga, 2005) may soon become reality (Haynes and Rees, 2006). In relation to deception, expectations and research have focused on systems that can accurately detect deceit from brain activation contrasts or pattern analysis, perhaps in connection with other physiological measures (Kozel et al., 2009; Langleben and Moriarty, 2013). These would help reduce uncertainty and provide information otherwise undetectable to the interviewer. By making the interviewee's brain *more accessible* they would artificially augment the interviewer's detection capabilities. Moreover, they would provide essential information about the localization of deception-relevant brain activity for individually targeted deception modulation tools (see e.g., Bohning et al., 2004). It may be easy to create expectations about potential advantages for the criminal justice system and security at large if such an enterprise were to actually succeed. For example, it could be claimed that it will be possible to accurately discriminate between genuine and concocted eyewitness testimony (Azar, 2011), more judiciary decisions could be based on objective evidence, and trials would become more expedite. Culprits would be less likely to elude unmasking and arguably more likely to be found guilty; crime rates may drop; and organized crime which relies on member loyalty could be more penetrated.[1] On its face, and without critical analysis, the benefits cited here might be presented as both obvious and great in number.

Expectations within deception research are by no means limited to the development of reliable lie detectors. Indeed noninvasive brain stimulation (e.g., tDCS and TMS) may soon offer both a new, upgraded alternative to truth serums by enabling the user to interfere with activity in brain regions that are causally related with deception (e.g., Priori et al., 2008; Karton and Bachmann, 2011), as well as its counterpart; a portable deceit enhancer (Karim et al., 2010; Mameli et al., 2010; Karton and Bachmann, 2011; Fecteau et al., 2013). It is easy to imagine the enormous advantages for counterespionage, policing, and diplomacy if a "deception inhibitor" was available. In extreme scenarios, interrogations would become more humane; negating the need for more outrageous practices such as sleep-deprivation, electric shocks, nail pulling, water-boarding, and so forth, to weaken psychophysical defense mechanisms and coerce the disclosure of information (see e.g., Tarabay, 2014, and the documentary Standard Operating Procedure, 2008). In more ordinary cases, this induced cooperation would make criminal justice mechanisms more agile and cost-effective. Potentially more guilty individuals will confess and be rightfully convicted.

Similarly, it is arguable that difficult diplomatic negotiations could benefit from both sides employing "deception inhibitors". These may decrease the capability of either side negotiating in bad-faith by concealing their true thoughts (though it is equally likely such devices may make parties reluctant to enter into negotiations to begin with). Conversely "deception boosters" would conceivably be invaluable in the hands of private and governmental agencies concerned with security, policing, espionage, and diplomacy. Undercover agents might be better able to conceal their true identities, and negotiators better equipped to convincingly promote positions they knew to be false.

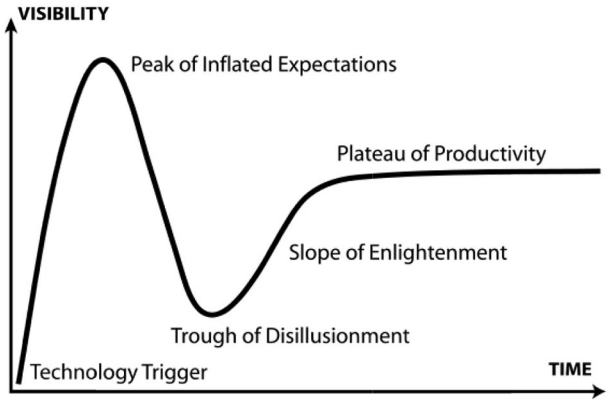

FIGURE 1 | The Gartner Hype Cycle (van Lente et al., 2013).

HYPE: THE DOWNSIDE OF EXPECTATIONS

While expectations such as these play important roles in achieving scientific and technological advancements, we must acknowledge an inherent fundamental limitation: expectations may be unreliable as predictors of the future (Brown and Michael, 2003). Even when high expectations for future advancements are shared by a large multidisciplinary community of scientists enjoying both support and resources, this does not guarantee scientific success (Pollock and Williams, 2010; Tutton, 2011). The failure of a scientific or engineering endeavor to meet its expectations leads to accusations of *hype*. Used in this way hype is referring to unrealistic, unattainable expectations; hence it is often only a distinction in framing that separates expectations from hype. What follows the characterization of (positive) expectations as (negative) hype is usually a period of disappointment or disillusionment. Enthusiasm for the proposed scientific advancement plummets as a result of expectation not being met, possibly followed by a gradual form of recovery. This process is referred to as a hype-disappointment cycle (van Lente et al., 2013). The Gartner hype cycle (see **Figure 1**), employed by the analyst firm Gartner Inc. is probably the most recognized model employing this concept. Note that under this model, the failure of scientific research or technological development to meet its initial expectations does not mean it is automatically and permanently discarded; rather that it is subject to a period of slower development towards more realistic goals.

This process, whereby (what in hindsight proved to be exaggerated) expectations were employed to secure support for research only to be followed by an abrupt collapse, has repeated itself in a multitude of past technologies; including hydrogen-powered cars (Bakker, 2010), nanotechnologies (Ebeling, 2008), and genomics

[1]See http://www.fbi.gov/about-us/investigate/organizedcrime

(Bubela, 2006). No scientific discipline is immune from such outcomes, and some expectations for the promise of brain imaging and modulation will almost inevitably suffer the same result to some extent (see e.g., Walsh, 2013). The likelihood of this occurring is growing as neuroscientists increasingly push the boundaries of what they are presenting as realistic research outcomes in their efforts to secure support and resources for their research. Indeed in Gartner's (2013) Hype Cycle for Emerging Technologies, *human augmentation* (which would include brain augmentation) is specifically identified as a technology currently *on-the-rise* towards its peak of inflated expectations (Gartner, 2013). It has also been suggested that *functional neuroimaging* technologies may be even further advanced along the classic Hype Cycle trajectory than augmentation (Rachul and Zarzeczny, 2012). One example from neuroscience justifying this characterization is the potential use of fMRI in the detection of deception.

More than a decade on since the first peer-reviewed empirical reports on deception detection in fMRI (see e.g., Spence et al., 2001; Langleben et al., 2002; Ganis et al., 2003), the field has seen incremental advances both in the "brain-reading" technique and in the refinement of cognitive testing protocols (see e.g., Sartori et al., 2008; Moreno, 2012; Wright et al., 2012; Park and Friston, 2013). Multiple patent applications have been filed but the envisioned fMRI deception detector looks still far from becoming reality. We have highlighted elsewhere a series of hurdles that an fMRI-based deception detector would need to surmount before it can succeed (Rusconi and Mitchener-Nissen, 2013). These include scientific hurdles such as; the assumptions and inferences underlying fMRI processes, the need to achieve consistent internal validity, manipulation of results by subjects, and the difficulty in moving beyond the laboratory setting. Also included were legal and ethical hurdles, such as; possible human rights violations, the issue of compelled questioning, the probative value of such evidence, and how the right to a fair trial would be impacted. It is open for debate whether or not its stimulation counterpart stands a better chance to translate into an applied deception modulator tool. One obvious advantage is that certain stimulators are both portable and affordable; however the science is probably not mature enough to justify its near-medium term expectations. The reported modulatory effects (facilitation or interference) obtained in controlled laboratory settings are statistically significant but rather minuscule in a standard interrogation context and short-lived, thus as things stand the gains may not eventually justify the efforts. This consideration only applies to applicative expectations—not to the utility and importance of such research within basic science. The in-lab testing protocols have not been validated against real-world situations (Luber et al., 2009), and the relation between modulation of deceits and its effects on other brain functions are still unclear, as is the role of individual differences (see Levasseur-Moreau et al., 2013 for a thorough discussion).

THE DOWNSIDE OF HYPE

The reason why neuroscientists should resist the temptation to over-hype the potential for brain augmentation is the detrimental consequences that can follow once unrealistic expectations are inevitably unmet. These include the following (see Brown, 2003; Ruef and Markard, 2010):

- Unrealistic short-term hype detracts from the long-term value of the basic science.
- Financial losses for corporate investors, and future difficulty in securing resources within fields which have suffered from a collapse of expectations.
- Resources are diverted from more realistically-achievable, yet less exciting, research programs.
- Undermined trust, which can slow or prevent future progress within a field of research.
- The reputations of individuals, companies/institutions, and entire research fields can suffer as past promises fail to materialize in the present.
- Identifiable people can suffer as a result; from individuals who suffer financial loss from investing in unrealistically over-hyped research programs, to patients who suffer emotionally having believed the claims that certain proposed brain augmentation techniques could treat their conditions.

In different combinations, these detrimental consequences arise in the multitude of science and technology examples presented in the annual Gartner hype cycles, as well as the specific case-studies of hydrogen-powered cars, genomics, and nanotechnology discussed above.

Nevertheless, despite all these drawbacks of hype the temptation still remains to present the most ambitious expectations for scientific and technological research as something achievable in the future; be they time-slowing pills to replace prison sentences, portable reliable lie detectors, brain control devices, or extra-memory microchips. Perhaps unsurprisingly the probability of achieving these goals (which may be incredibly small) and the time-frame for doing so (which may be incredibly long) are afforded little discussion. The challenge facing neuroscientists is how to construct and present expectations that are less likely to cross that invisible barrier dividing "hope" from "hype".

ADDRESSING ETHICAL CONCERNS TO PRODUCE BETTER EXPECTATIONS AND THE RISKS OF NOT DOING SO

It is our contention that by reflexively considering the ethical, legal, and social impacts of a potential future technology or field of advancement, neuroscientists can improve the quality of the expectations they disseminate within their own field; thereby developing more nuanced, better expectations. This of course does not replace or neglects but is additional to the need for neuroscientists to educate the media, patients and research subjects about the potential and limits of neuroscience and neuroscientific techniques; to conduct enough studies and generate valid scientific data to know what neuroscience and these techniques can and cannot do. Before we develop this contention below, two points require expansion and clarification here. Firstly, we are characterizing these expectations as "better" if they constitute visions of the future constructed after taking into account existing legal regimes and concepts of human rights,

ethical norms, and attitudes of societies into which they are expected to operate. Secondly, it should also be emphasized that the stage we are referring to is the formulation and presentation of initial expectations by the scientists. This stage often precedes wider public/multi-stakeholder engagement and the development of respective communication strategies (for more detailed discussions of such topics see: Jasanoff, 2003; O'Doherty and Einsiedel, 2012; Bucchi and Trench, 2014; Stilgoe et al., 2014).

The concomitant social, legal and ethical implications of a proposed scientific/technological expectation are often neglected at the initial stage of its formulation and proposition. Hence what is often initially presented is the envisioned advancement free from ostensibly non-scientific constraints; i.e., presenting the expectations of a pill that slows one's perception of time or of the portable lie detector device, but doing so free from any contextual discussion. This may occur for a number of reasons, including: (a) because no ethical/legal/social implications exist (highly unlikely for most expectations); (b) those presenting these futures have not considered and/or foreseen such implications; (c) these implications are viewed as either unimportant or not the responsibility of the scientist involved; and/or (d) there is a fear that by acknowledging the existence of such implications, the advancement in question will be viewed less positively thus putting at risk the benefits expectations can bring to a research program.

However, failing to reflexively consider the ethical, legal, and social impacts of a potential future technology or field of advancement does not negate their existence or make them disappear. These factors are going to have to be addressed at some point in the research and development lifecycle of a new technology for scientific advancements do not develop or exist separately to the societies in which they operate (see MacKenzie and Wajcman, 1999). We contend that both the benefits of engaging in this reflexive process early in the development of new expectations, as well as the potential negative implications of failing to do so, make this early consideration of ethical, legal, and social impacts an essential step in their development.

By considering ethical, legal, and social impacts to create "better" expectations, neuroscientists gain a number of advantages. They can act to avoid their expectations becoming characterized as hype. They can identify sources of possible controversy and resistance within their proposed expectations, thereby affording them the opportunity to consciously address such issues both through how they formulate their expectations and how they seek to present them. Also by mitigating the propensity for individuals or societal groups to actively criticize or resist their expectations, the neuroscientist is effectively maximizing their potential network of future supporters.

Failure to create "better" expectations can have specific negative consequences. It can shift expectations into the realm of hype (the inherent negative consequences of such were discussed earlier). It has also been posited that by presenting technological expectations unfettered by non-technical considerations (such as ethics, legality, and social acceptability), critics can more easily create counterarguments by presenting dystopian futures involving them (see Tutton, 2011). Essentially the argument here is that; if the presentation of an expectation devoid of some inherent moral character justifies utopian visions of its future use, then dystopian visions of its future use are also equally valid (see Pickersgill, 2011 for a practical example of this argument in relation to *neuro-law*).

Furthermore, by promoting a real-world version of, and uses for, a future technology absent of a robust consideration of social, legal and ethical issues is to promote a tool that is more easily open to legitimate social, legal and ethical criticism. We believe this advice has resonance for many of the expectations currently being espoused by neuroscientists within the field of neuroimaging and brain modulation; from enhancing the cognitive potential of users, to brain control/manipulation, to increasing/decreasing the capacity of an individual to deceive. An important point here is that each expectation must be individually reflexively examined, for the nature of these social, legal and ethical criticisms will differ depending on the specific application that is being envisaged. This diversity means there are no shortcuts to robust reflexive examinations. For example, in the case of fMRI deception detection in criminal proceedings discussed above, we examined in depth how future expectations of this advancement conflicted with existing legal and human rights regimes, as well as social and ethical norms. This led us to conclude that "[c]ognitive neuroscientists must be careful not to over-play what these technologies can offer criminal courts nor their vision of the potential future role of neuroscience within criminal courts, lest they overplay themselves out of the courtroom altogether" (Rusconi and Mitchener-Nissen, 2013, p. 9). Conversely, the main hurdles of brain reading and modulation may be characterized as: legal and human rights issues over compelled questioning, fair trials, and the probative weight attached to such evidence; as well as the social implications of undermining our naturally evolved capacity to deceive. Whereas those raised by cosmetic enhancement include: the ethicality of altering fundamental elements of self-identity; social justice concerns over the inequitable distribution of cognitive enhancement techniques; the undermining of autonomy; and determining the "proper" role of enhancement technologies in society (Wolpe, 2002; Hamilton et al., 2011). Given the mounting emphasis on "impact", even from government founding agencies that have traditionally encouraged basic research, neuroscientists may need some assistance in this reflexive process. This could be offered in the form of further training and multidisciplinary education opportunities or direct access to professional figures with the relevant expertise. On the other hand, funding agencies and scientific journals could also be required to closely monitor and develop awareness of the more hype-prone research areas, as their endorsement (sometimes motivated by the immediate visibility that inflated expectations can grant) may play a role in amplifying, rewarding and maintaining hype within the scientific community.

CONCLUSION

Expectations are presented as a valuable tool for neuroscientists in acquiring both resources and networks of allies to assist in converting these expectations into reality. However, in applying

the often-used adage of caution, that "if a little bit of something is good then a lot is not necessarily better", unrealistic expectations can become synonymous with hype which in turn can threaten the very programs the scientists are seeking to promote. Similarly, promoting the expectation of a scientific or technological advancement free from any social, legal or ethical considerations will not benefit that advancement. For any critical assessment will easily be able to identify these non-technical concerns which neuroscientists have ostensibly ignored; again placing at risk the programs they are seeking to advance.

Provided they are supported by (and are not used as a replacement for) sound research on the safety and efficacy of neuroscientific techniques, expectations *are* a valuable resource for capturing the public's imagination and promoting investment in an area for research. We encourage those neuroscientists working in the field of neuroimaging and brain modulation, with its exciting prospects for the future, to employ this valuable resource as they would any other at their disposal to help further their research goals. We simply caution that when doing so, if they present expectations that are disassociated from any measure of realism, or treat the concomitant legal, social and ethical considerations as optional extras, then hype (and Gartner's *Trough of Disillusionment*) surely awaits.

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