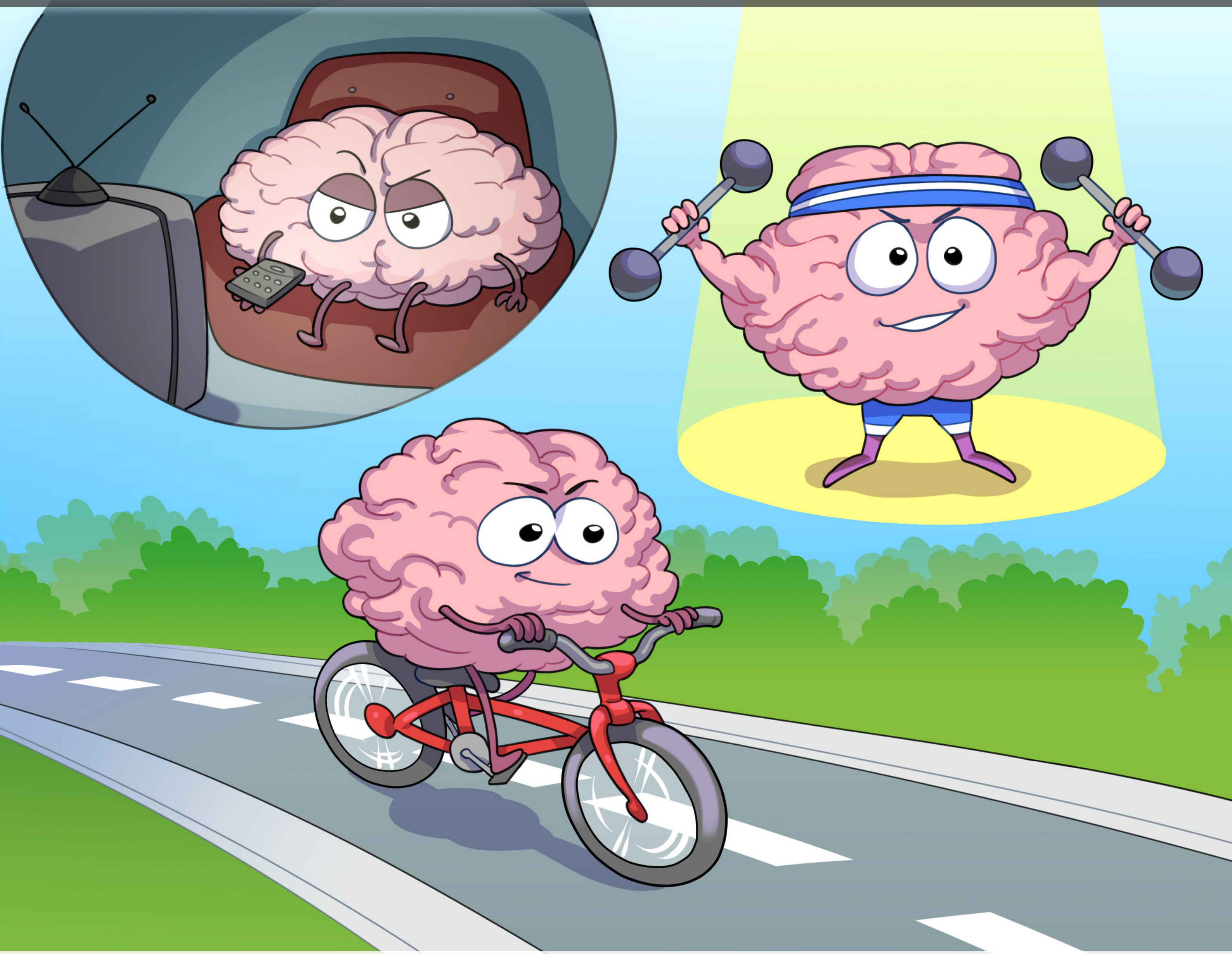
MIND-BRAIN PLASTICITY AND REHABILITATION OF COGNITIVE FUNCTIONS: WHAT TECHNIQUES HAVE BEEN PROVEN EFFECTIVE?

EDITED BY: Katiuscia Sacco and Benedetto Sacchetti

PUBLISHED IN: Frontiers in Behavioral Neuroscience



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-187-6
DOI 10.3389/978-2-88945-187-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

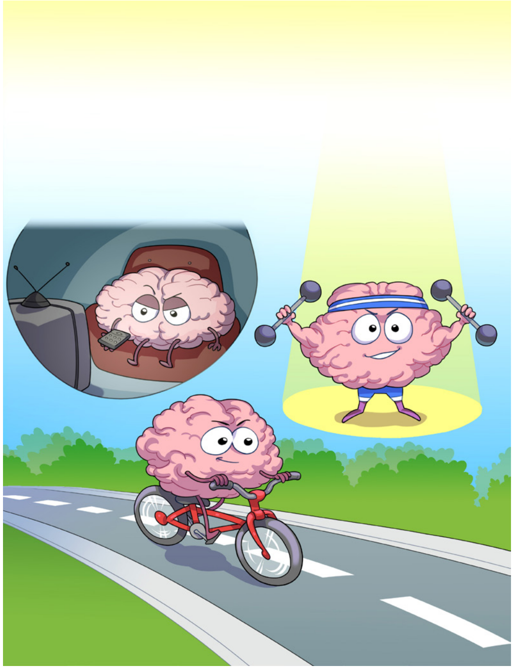
Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

MIND-BRAIN PLASTICITY AND REHABILITATION OF COGNITIVE FUNCTIONS: WHAT TECHNIQUES HAVE BEEN PROVEN EFFECTIVE?

Topic Editors:
Katiuscia Sacco, University of Turin & Neuroscience Institute of Turin, Italy
Benedetto Sacchetti, Neuroscience Institute of Turin & University of Turin, Italy



Black Flamingo srl - Flavia Mormile

Citation: Sacco, K., Sacchetti, B., eds. (2017). Mind-Brain Plasticity and Rehabilitation of Cognitive Functions: What Techniques Have Been Proven Effective? Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-187-6

Table of Contents

frontiers in Behavioral Neuroscience

EDITORIAL
published: 20 December 2016
doi: 10.3389/fnbeh.2016.00232

Editorial: Mind-Brain Plasticity and Rehabilitation of Cognitive Functions: What Techniques Have Been Proven Effective?

Katiuscia Sacco [1,2]* *and Benedetto Sacchetti* [2,3]

[1] *Imaging and Plasticity Research Group, Department of Psychology, University of Turin, Turin, Italy,* [2] *Neuroscience Institute of Turin, Turin, Italy,* [3] *Department of Neuroscience, University of Turin, Turin, Italy*

Keywords: rehabilitation, plasticity, brain stimulation, training-induced changes, cognitive functions

Editorial on the Research Topic

Mind-Brain Plasticity and Rehabilitation of Cognitive Functions: What Techniques Have Been Proven Effective?

Contributions to this special issue represent an effective effort toward the understanding of how and to what extent rehabilitation drives neuronal changes, promoting recovery. **Table 1** summarizes all these studies.

A series of reviews have dealt with the efficacy of trainings aimed at the treatment of motor (Mateo et al.; Pazzaglia and Galli), visual (Sale and Berardi; Dundon et al.), sensory and (Bolognini et al.) and spatial disorders (Pedroli et al.).

Mateo et al. made an extensive review on motor imagery effectiveness during reach-to-grasp rehabilitation in spinal cord injury patients with tetraplegia. They found that motor imagery of possible non-paralyzed movements improved reach-to-grasp performance by increasing tenodesis grasp capabilities and muscle strength, decreasing movement time and trajectory variability, and reducing the abnormally increased brain activity. Moreover, motor imagery can be used to control brain-computer interfaces that successfully restore grasp capabilities.

Pazzaglia and Galli wrote a perspective study with the aim of translating novel findings in the perceptual and motor domains into the rehabilitation of movement disorders. Visual-motor approaches seem to maximize neural plasticity and lead to greater effect than visual inputs alone: according to the authors, this is because the first involve multiple sensory channels and thus enable individuals to better predict and optimize motor behavior.

Sale and Berardi reviewed interesting findings in adult rodents concerning the possibility of treating amblyopia, a severe visual function impairment which, until recently, has been effectively treated only in children, as there was no known way to foster adult visual cortex plasticity. Among the new proposed intervention strategies, non-invasive procedures based on environmental enrichment, physical exercise or visual perceptual learning appear particularly promising in terms of future applicability in the clinical setting.

Dundon et al. reviewed neuropsychological training methods of visual rehabilitation of homonymous visual field defects. They include "compensation" paradigms, which compensate vision loss by training eye scanning movements, and "restorations" paradigms, which activate residual visual functions by training light detection and discrimination of visual stimuli. The authors propose that both plasticity within peri-lesional spared tissue and changes between networks (i.e., recruiting alternative visual pathways) contribute to recovery.

OPEN ACCESS

Edited and reviewed by:
Nuno Sousa,
University of Minho, Portugal

Correspondence:
Katiuscia Sacco
katiuscia.sacco@unito.it

Received: *15 September 2016*
Accepted: *24 November 2016*
Published: *20 December 2016*

Citation:
Sacco K and Sacchetti B (2016) Editorial: Mind-Brain Plasticity and Rehabilitation of Cognitive Functions: What Techniques Have Been Proven Effective? Front. Behav. Neurosci. 10:232. doi: 10.3389/fnbeh.2016.00232

TABLE 1 | Assessment techniques and types of treatments.

Assessment technique	Behavioral	Behavioral and brain activity
TYPE OF TRAINING		
Behavioral	* Bolognini et al. (spatial and body representations, sensory and motor impairments) * Pedroli et al. (spatial, virtual reality, neglect) ° Ciaramelli et al. (memory, PFC lesions) ° Lévy-Bencheton et al. (vision, HVFD) ° Livelli et al. (multi-domains, HIV/AIDS NCD) ° Mattioli et al. (central executive functions, MS) °° Panerai et al. (multi-domains, NCD)	* Sale and Berardi (vision, rodents) * Dundon et al. (vision, HVFD) * Mateo et al. (motor, SCI) # Costa et al. (BDNF, executive domains, Parkinson + MCI) # Kamran et al. (fNIRS) °° Sacco et al. (communication, TBI) ° Tsai and Wang (executive functions, elderly)
Nervous System Stimulation	° Bisio et al. (motor, PNS, healthy) ° de Aguiar et al. (language, tDCS, aphasia)	* Pazzaglia and Galli (visuo-motor, movement disorders) ° Chaieb et al. (motor learning, tNIRS, healthy) ° D'Agata et al. (motor, rTMS, tDCS, stroke) ° Sacco et al. (attention, tDCS, TBI)

BDNF, brain-derived neurotrophic factor; fNIRS, functional near-infrared spectroscopy; HVFD, Homonymous visual field defects; MCI, mild cognitive impairment; MS, multiple sclerosis; NCD, neurocognitive disorder; PFC, prefrontal cortex; SCI, spinal cord injury; TBI, traumatic brain injury; tDCS, transcranial direct current stimulation; tNIRS, transcranial near-infrared stimulation.
° *Individual sessions.*
°° *Group sessions.*
Biomarker research; Model development.
* *Review/Perspective study.*

Bolognini et al. produced a mini-review to show how crossmodal illusions—products of multisensory integration—can be used in rehabilitation settings to restore disarranged spatial and body representations related to pain, sensory, and motor impairments, as well as their use for improving neuroprosthetics.

Pedroli et al. carried out a systematic review of the most recent virtual reality applications for the assessment and rehabilitation of unilateral spatial neglect, providing crucial indications for neurorehabilitation interventions and clinical practice.

Two papers presented biomarker research and model development.

Costa et al. showed a significant positive correlation between brain-derived neurotrophic factor (BDNF) serum levels and cognitive functioning in attention and executive domains in 13 Parkinson's disease patients with mild cognitive impairment. Given the role of BDNF in regulating synaptic plasticity, this trophic factor may be a potential biomarker for evaluating cognitive changes in neurological syndromes associated with cognitive decline.

Kamran et al. working with functional near-infrared spectroscopy (fNIRS), developed an hemodynamic response model able to estimate inter-subject variations in HRF and physiological noises for better cortical functional maps.

A series of research papers looked at behavioral changes as a consequence of behavioral treatments.

Lévy-Bencheton et al. studied 14 left- or right homonymous visual field defect patients with a training based on a single 15 min voluntary anti-saccades task toward the blind hemifield. When combined with an adaptation paradigm, letting automatic sensorimotor adaptation to increase AS amplitude, it improved visual quality of life while exploring visual scenes or reading a text.

Livelli et al. tested a 4 month cognitive rehabilitation protocol on 16 HIV/AIDS patients with HIV-associated Neurocognitive Disorder (HAND), compared to 16 HIV/AIDS without HAND. The experimental group showed cognitive improvements in various domains: those in Abstraction/executive functioning and in Attention/working memory were still present at the 6 month follow up. On the contrary, the control group significantly worsened in the same domains.

Mattioli et al. evaluated the efficacy of a 15 week domain specific cognitive training, compared to a specific psychological intervention, in 41 patients with multiple sclerosis, showing that, at 2 years follow up, patients' submitted to the specific training improved in the majority of the cognitive tests and ameliorated their perceived cognitive performance.

Ciaramelli et al. tested the Preview-Question-Read-State-Test method, a technique used to enhance long-term memory when reading a text, in 7 patients with mild memory problems due to prefrontal cortex lesions, showing that it improves immediate and delayed recall, as well as the ability to answer questions of comprehension. The same improvement is present both when the experimenter formulated the questions about the text, and when the patients did it on their own.

Panerai et al. carried out a daily group Intensive Cognitive Activation protocol, over a period of 2 months, in 16 patients with major neurocognitive disorder (NCD) and 15 with mild NCD; a control group of 11 patients with major NCD was used as a control group. General cognitive functioning and other specific functions, including attention, ideomotor praxis and visual memory, improved in all patients. Besides, while long- and short-term verbal memory worsened in controls, they did not in the experimental groups.

Two research papers looked at behavioral changes as a consequence of nervous system stimulation.

Bisio et al. showed, on 48 healthy participants, that spontaneous movement tempo—the movement freely produced by subjects tapping out a rhythm with their fingers—can be modified by action observation (AO) combined with peripheral nerve stimulation (PNS), even in absence of immediate movement execution. The induced changes in spontaneous movement tempo, attributable to neuroplasticity mechanisms, indicate possible application of AO-PNS in rehabilitative treatments.

de Aguiar et al. showed that a linguistically-motivated language therapy focusing on verb inflection and sentence construction, combined with transcranial Direct Current Stimulation (tDCS), is effective in producing both item-specific and generalized improvement in 9 individuals with post-stroke aphasia.

Two research papers looked at behavioral and brain activity changes as a consequence of behavioral treatments.

Sacco et al. proposed a group training program for the rehabilitation of communicative abilities and tested it on 8 traumatic brain injury patients, showing an improvement in overall communicative performance which was still present 3 months later. Besides, they found increased amplitude of low frequency fluctuation, measured through resting state functional magnetic resonance imaging (fMRI), in brain regions involved in communication.

Tsai and Wang studied 64 elderly individuals, divided in three groups, showing that physical exercise reduces reaction times during a task-switching paradigm with unpredictable and infrequent switches, and it enhances electrophysiological response related to executive functioning (P2 and P3 amplitudes). It seems that open-skill exercise has a small advantage on executive control with respect to closed-skills.

Finally, three papers dealt with behavioral and brain activity changes as a consequence of brain stimulation treatments.

Chaieb et al. studied the neuroplastic effects of transcranial near-infrared stimulation (tNIRS) on the motor cortex in healthy participants. The serial reaction time task was used to investigate the possible effect of tNIRS on implicit learning. A significant decrease in the amplitude of motor-evoked-potentials (MEPs) was observed up to 30 min post-stimulation. Furthermore, the short interval cortical inhibition was increased and facilitation decreased significantly after tNIRS. Such results have to be taken into account when using tNIRS to elicit plastic changes in TBI or stroke patients.

D'Agata et al. used Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS), for upper limb rehabilitation of 34 patients with stroke, showing that the effects of the two techniques are comparable, with some advantages using tDCS versus rTMS. They also found that more than one cycle (2–4 weeks), spaced out by washout periods, should be used, only in responder patients, to obtain clinical relevant results.

Sacco et al. showed that 10 sessions of transcranial direct current stimulation (tDCS), each followed by computer-assisted training, improved divided attention in 16 traumatic brain injured (TBI) patients, compared to 16 TBI for whom the training was preceded by sham stimulation.

Functional magnetic resonance imaging (fMRI) data showed neural changes, interpreted as normalization of previously abnormal hyperactivations.

AUTHOR CONTRIBUTIONS

KS drafted the Editorial and BS approved it for publication.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MINI REVIEW
published: 10 August 2015
doi: 10.3389/fnbeh.2015.00212

Crossmodal illusions in neurorehabilitation

Nadia Bolognini[1,2,3]*, *Cristina Russo*[1,3] and *Giuseppe Vallar*[1,2,3]

[1] Department of Psychology, University of Milano-Bicocca, Milan, Italy, [2] Laboratory of Neuropsychology, IRCSS Istituto Auxologico Italiano, Milan, Italy, [3] NeuroMi – Milan Center for Neuroscience, Milan, Italy

In everyday life, many diverse bits of information, simultaneously derived from the different sensory channels, converge into discrete brain areas, and are ultimately synthetized into unified percepts. Such multisensory integration can dramatically alter the phenomenal experience of both environmental events and our own body. Crossmodal illusions are one intriguing product of multisensory integration. This review describes and discusses the main clinical applications of the most known crossmodal illusions in rehabilitation settings. We consider evidence highlighting the contribution of crossmodal illusions to restore, at least in part, defective mechanisms underlying a number of disorders of body representation related to pain, sensory, and motor impairments in neuropsychological and neurological diseases, and their use for improving neuroprosthetics. This line of research is enriching our understanding of the relationships between multisensory functions and the pathophysiological mechanisms at the basis of a number of brain disorders. The review illustrates the potential of crossmodal illusions for restoring disarranged spatial and body representations, and, in turn, different pathological symptoms.

Keywords: crossmodal illusions, neurorehabilitation, multisensory, body representation, pain, motor disorders, sensory disorders

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Francesca Garbarini, University of Turin, Italy
Francesca Frassinetti, University of Bologna, Italy

Correspondence:
Nadia Bolognini, Department of Psychology, University of Milano-Bicocca, Building U6, Piazza Dell'Ateneo Nuovo 1, 20126 Milano, Italy
nadia.bolognini@unimib.it

Received: *24 April 2015*
Accepted: *28 July 2015*
Published: *10 August 2015*

Citation:
Bolognini N, Russo C and Vallar G (2015) Crossmodal illusions in neurorehabilitation. Front. Behav. Neurosci. 9:212. doi: 10.3389/fnbeh.2015.00212

Introduction

In everyday life, we are surrounded by a plethora of different sensory signals that concurrently hit our senses. Although our first-hand perception seems dominated by a single modality, commonly vision (Wade and Swanston, 2001), different sensory signals are simultaneously processed and integrated. In this way, without any conscious effort, perceptual and cognitive functions, as well as the underlying brain activity, are shaped by interactions between senses. The brain is endorsed with specialized neural and cortical mechanisms for the synthesis of information derived from the different senses into coherent, unitary representations that guarantee adaptive behavioral responses (Stein and Meredith, 1993; Driver and Noesselt, 2008). The primary advantage of multisensory integration consists in the enhancement of the salience of sensory stimuli, which, in turn, facilitates behavioral responses to them, as, for instance: fastening spatial orienting, improving memory and language comprehension, optimizing sensorimotor control (Bolognini et al., 2005; Alais et al., 2010). Multisensory facilitatory effects typically arise through the processing of congruent sensory signals. However, our brain also tends to impose coherence to discordant sensory information. This process may give rise to crossmodal illusions. Indeed, the way we perceive signals from our own body, or from the external space, can be conceived as the output of brain processes, based on an informed interpretation of the stimuli. Crossmodal illusions occur when what we sense with one modality affects what we experience in another modality. Seen in this perspective, crossmodal illusions represent perceptual strategies for dealing with inter-sensory conflicts, ultimately aimed at giving coherence to the on-going perceptual experience. Remarkably, this function does not result from inferential, or other higher-level "cognitive" processes, such as deploying a decision strategy for responding to ambiguous or conflicting experiences; rather, it is based on automatic multisensory interactions in the brain, which occur largely outside the realm of conscious perception. Two basic mechanisms have been proposed as to how multisensory interactions can affect perception. First, feedback projections from higher-order association regions of the cortex provide a way for information regarding one modality (e.g., vision) to influence sensory processing at putatively unisensory cortical stages, committed to a different modality (e.g., touch); alternatively, feed-forward anatomical connections between primary sensory-specific areas may allow a fast exchange of sensory information at lower-level stages of cortical processing (Driver and Noesselt, 2008; Cappe et al., 2009).

In recent years, there has been an explosion of research on crossmodal illusions, which has attempted at unravelling how multisensory interactions shape human perception and cognition. Crossmodal illusions have been applied also in clinical populations. In neuropsychological research, for instance, crossmodal illusions have been used to look for evidence of disrupted or abnormal multisensory integration in patients with acquired focal brain lesions, using anatomo-clinical data to infer associations between the site of a brain lesion, the resultant multisensory disorder, and findings from neuroimaging experiments in healthy humans (for a review of this line of research see Bolognini et al., 2013a). The present review considers another intriguing field of research, concerned with the possibility of using crossmodal illusions as tools for rehabilitation. Here, we focus on the two most renowned crossmodal illusions applied with clinical purposes, the Mirror Box and the Rubber Hand illusions, illustrating their efficacious use for the treatment of pain (phantom limb pain, complex regional pain syndrome, spinal cord injury), and post-stroke motor, spatial, and bodily impairments (hemiparesis, visuo-spatial neglect, somatoparaphrenia, anosognosia for hemiplegia, alien hand syndrome); finally, their potential for optimizing neuroprosthetics is discussed.

Therapeutic Applications of Crossmodal Illusions

Mirror Box Illusion

The Mirror Box Illusion (MBI) is one of the most famous crossmodal illusions (Ramachandran and Altschuler, 2009; Lamont et al., 2011). The MBI is generated by a visual-motor conflict: when participants move one hand in front of a parasagittal mirror, while the other hand is kept behind the mirror, hidden from view, they may experience the illusion of symmetrical bimanual movements, as well as other illusory kinaesthetic and motor effects on the hidden limb (e.g., Altschuler, 2005; Snijders et al., 2007; Romano et al., 2013). Watching the mirror reflection of own movements also increases the excitability in the motor cortex, ipsilateral to the moving hand (Garry et al., 2005). Additionally, the mismatch between the movement performed by participants and the movement they observe increases neuronal activity in areas associated with self-awareness and spatial attention (i.e., precuneus, posterior cingulate and posterior parietal cortices; Fink et al., 1999; Dohle et al., 2004; Matthys et al., 2009; Michielsen et al., 2011a; Nojima et al., 2012).

The first clinical application of the MBI has been for alleviating Phantom Limb Pain (PLP) after amputation (Ramachandran et al., 1995). Melzack (1992) first proposed a central role of multisensory integration of bodily signals by the so-called "neuromatrix" in the construction of the body image and the generation of pain. When, through the mirror reflection, the intact arm is superimposed on the phantom limb, patients report the sensation that they can move and relax the cramped phantom limb, and experience pain relief. In this framework, relief from PLP presumably results from the correction of the incongruence between motor output (intention) and sensory (proprioceptive) feedback, brought about by the visual input of movements of the missing limbs. As a consequence, the "latent" cortical map of the missing limb may be re-activated (Moseley et al., 2008; Ramachandran and Altschuler, 2009; Moseley and Flor, 2012). Moreover, the sensory-motor conflict generated by the MBI can modulate motor cortical excitability, which is altered in many patients suffering from chronic pain of central origin (Lefaucheur, 2013; Bolognini et al., 2015). However, not always moving the phantom limb diminishes PLP: in some amputees the phantom movement can actually increase PLP (cramping sensations). Therefore, an alternative version of the MBI has been developed, whose main feature is that patients look at the mirror reflection of touches applied to the intact hand, while receiving touches on the stump positioned behind the mirror (Schmalzl et al., 2013). The induction of illusory touch on the phantom hand effectively reduces PLP in patients who do not respond to the standard MBI. Hence, different inter-sensory conflicts may be appropriate for amputees with different types of phantom sensations: while the MBI is effective for reinstalling voluntary movements of paralyzed phantoms, and release concomitant clenching sensations, the visual-tactile version of the MBI is useful for patients who can voluntarily move their phantom, but tend to experience a concomitant increase in cramping sensations (Schmalzl et al., 2013).

Besides PLP, successful use of MBI has been reported in patients with other pain syndromes, such as the Complex Regional Pain Syndrome, and even in sensory re-education of severe hyperesthesia after hand injuries (Moseley and Flor, 2012). The finding of analgesic effects of the MBI across different pain disorders is suggestive of a common pathophysiological mechanism, linked to defective or altered multisensory processing, which can be regulated by the sensory-motor conflict of the MBI. Chronic pain is indeed associated with the disruption of a range of multisensory body-related cortical representations, which, in turn, reflects maladaptive neuroplastic changes in the brain.

One recent development of MBI for pain relief concerns its combined use with transcranial Direct Current Stimulation (tDCS) of the motor cortex. Different physiological mechanisms mediate the analgesic action of motor cortex stimulation by tDCS, which share some similarities with those of the MBI, namely: modulation of motor cortex excitability and changes in perceptual and emotional processing of the pain experience (Brunoni et al., 2012; Knotkova et al., 2013). Therefore, the use of tDCS as an add-on intervention to MBI could potentiate its antalgic action. This strategy was applied in patients with neuropathic pain following Spinal Cord Injury (Soler et al., 2010): tDCS over the motor cortex was delivered during a modified version of the MBI, consisting in a virtual reality procedure to induce a visual illusion of walking. The combined use of tDCS and MBI reduced the overall severity of pain, as well as improved various subtypes of neuropathic pain (continuous and paroxysmal pain, mechanical allodynia and dysaesthesias) in patients with spinal cord injury, with greater and longer-lasting effects than those induced by each single intervention (tDCS or MBI).

Another well-known application of the MBI is for the rehabilitation of hemiparesis in stroke patients (e.g., Altschuler et al., 1999; Dohle et al., 2009; Ramachandran and Altschuler, 2009; Michielsen et al., 2011b; Thieme et al., 2013). Although the precise mechanisms whereby MBI contributes to post-stroke motor recovery are still unclear, neuroimaging data highlight the key role of the sensory-motor mismatch (Michielsen et al., 2011a). Watching the reflection of self-generated movements in the mirror increases attentional demands for the integration of vision and proprioception, induced by the mirror, and neural activity in multisensory areas associated with self-awareness and spatial attention. These effects may translate into an increased awareness of the affected limb, which may counteract learnt non-use (Michielsen et al., 2011a,b). This hypothesis is also supported by evidence showing beneficial effects of the MBI on unilateral visuo-spatial neglect (Dohle et al., 2009). In this case, watching self-induced movements in the left side of space, contralateral to the side of the hemispheric lesion (contralesional), may facilitate leftward visuo-spatial orienting, impaired in left spatial neglect, and awareness of events occurring in the left, neglected, side of space. Noteworthy, self-observation in a mirror is also useful for ameliorating somatoparaphrenia, a somatic delusion usually following right-hemisphere lesions, which typically manifests as a defective sense of ownership of the patient's left, contralesional, body parts (Fotopoulou et al., 2011; Jenkinson et al., 2013). Finally, "off-line" self-observation in a video replay reinstates motor awareness in patients with anosognosia for hemiplegia, speeding up recovery (Fotopoulou et al., 2009).

Recently, the MBI has been used to improve disorders of motor control, such as the Alien Hand Syndrome (AHS). The AHS is a higher-order disorder of motor control featured by involuntary, yet purposeful, movements of the affected limb, typically the hand, which may follow infarction in the vascular territory of anterior cerebral artery, midline tumors, and neurodegenerative illnesses. The impaired voluntary motor control in the AHS has been proposed to be due to a pathological neurofunctional disconnection between motor intentions and sensory information. Following this line of reasoning, in one patient with right AHS due to an intracerebral hemorrhage in the left fronto-parietal cortex, the MBI was used for restoring the congruency between motor intentions and visual feedback, consequently improving the voluntary fine motor control of the alien hand (Romano et al., 2014).

Rubber Hand Illusion

The Rubber Hand Illusion (RHI) is another crossmodal illusion widely investigated in clinical settings (Botvinick and Cohen, 1998), although its application in rehabilitation is still in an early stage (Christ and Reiner, 2014). The RHI is induced by brushing a person's hand, hidden from view, while synchronously brushing a visible rubber hand. This results in a sense of ownership of the rubber hand, and in a projection of sensations from the brushed rubber hand to the person. The RHI is also associated with a measurable proprioceptive drift in the perceived location of the hand towards the rubber hand, and changes in reaching movements performed with the stimulated hand (Tsakiris and Haggard, 2005; Kammers et al., 2010). The RHI has been used to uncover mechanisms of body ownership, the plasticity of body representations, and their dependency on multisensory integration of touch, proprioception, and vision. Deficient body ownership is the hallmark of somatoparaphrenia, which therefore represents the optimal condition for assessing the chance of manipulating and, possibly, restoring a deranged multisensory representation of the body concerned with self-representation and body-part ownership (Vallar and Ronchi, 2009). In one study in two right-brain-damaged patients with a stable somatoparaphrenia, we first applied the classical RHI paradigm to verify whether multisensory mechanisms supporting the sense of body-part ownership were disrupted, notwithstanding the patients' pathologic delusion for their left hand (Bolognini et al., 2014; see also Jenkinson et al., 2013). Both patients proved to be susceptible to the RHI to the same extend as healthy subjects: this suggests undamaged multisensory mechanisms for the synthesis of bodily signals concerned with body ownership. In the light of such evidence, we investigated whether the RHI could also induce a remission of the delusional beliefs concerning the left hand. This hypothesis was tested with a modified version of the RHI, which consisted in stroking both the patient's visible (disowned) left hand, and the right hand, hidden from view. Notably, patients could not report the feeling of being touched during stroking of their left hand, due to a co-occurring hemianesthesia. Our manipulation induced an immediate self-re-attribution of the left hand, with one patient showing a long-lasting remission of the somatic delusion. This evidence indicates that the multisensory representation of the body concerned with ownership, deranged as a somatic delusion in somatoparaphrenia, is not completely lost, as indicated by its restoration by multisensory bodily stimulations in the form of the RHI, which allows regaining the sense of ownership of the disowned hand.

The use of RHI in the Complex Regional Pain Syndrome (Reinersmann et al., 2013) and in Cervical Spinal Cord Injury (Lenggenhager et al., 2013) is based on a similar line of reasoning. In both these conditions, the RHI can be used to improve tactile awareness and processing, likely by reactivating tactile memories, and restoring an altered bodily self-representation, that may follow impaired sensorimotor abilities. The RHI is also useful for the treatment of chronic pain in these disorders, considering the tight link between pain and body image distortions along with disruption of a range of body-related cortical representations (Lotze and Moseley, 2007).

The aim of using the RHI to strengthen spatial and body awareness has guided its application in patients with unilateral visuo-spatial neglect. In a right-brain-damaged patient, immediately after the induction of the RHI (with the rubber hand located in the left side of space), a short-lasting amelioration of left spatial neglect took place in letter cancellation and midline pointing tasks, with the patient experiencing a shift in the felt position of his right hand towards the left-sided rubber hand (Kitadono and Humphreys, 2007). The amelioration of visual neglect could be due to changes in the patient's egocentric reference frames, brought about the RHI, by cueing spatial attention, by modifying visuo-motor mapping, or by a combination of these different mechanisms. The susceptibility of patients with spatial neglect to crossmodal illusions suggests that multisensory integration is largely spared in this neuropsychological syndrome (Bolognini et al., 2013a), despite the possible presence of modality-specific attentional disturbances, which may impact perceptual awareness in different sensory modalities (Vallar and Bolognini, 2014).

Another field of application of the RHI concerns neuroprosthetics, where the major goal is to develop artificial limbs that feel like a real part of the body. Here, the RHI was used to favor, in a simple and non-invasive way, the embodiment of the prosthesis, re-creating a coherent representation of the body, and producing tactile sensations in the prosthetic limb in amputees. Indeed, for a limb to be functionally useful one must be able to sense not only movements, but even touch; additionally, the acceptance of the prosthesis as one's own body-part influences the overall well-being of the amputee (Gallagher and MacLachlan, 1999). In upper limb amputees, the RHI can be induced by simultaneously touching the stump and the finger of the prosthesis; this elicits an illusion of sensing touch on the artificial hand and a feeling of ownership of it (Ehrsson et al., 2008; Rosén et al., 2009). A similar approach was used in upper limb amputees with surgically redirected nerves (Marasco et al., 2011). Of note, such crossmodal manipulations with the prosthesis activate in amputees the same multisensory regions in the premotor cortex and the intraparietal sulcus involved, in healthy individuals, in the integration of visual, tactile and proprioceptive signals, on which the feeling of body ownership (Schmalzl et al., 2013), and phantom sensations (Bolognini et al., 2013b) are based. This supports the use of this crossmodal strategy to guide post-amputation cortical plasticity.

Discussion

The examples considered in this review indicate that "tricking" the brain with simple crossmodal illusions may offer an effective strategy to boost and wake up its multisensory capabilities, which may be latent or weakened by a brain disease. In this way, inter-sensory conflicts can restore altered sensory and motor representations subtending various disorders of body awareness, body ownership, movement, sensibility, attention and pain. Overall, these findings suggest that the brain may preserve its natural and basic tendency to integrate information from different sensory modalities in many pathological conditions, with crossmodal illusions resulting from hardwired perceptual organizing strategies or principles that, in general, are adaptive and advantageous. Such strategies involve rules for modulating experiential responses to multisensory information and rules that deal with important regularities (O'Callaghan, 2008), as ways for coping with environmental and corporeal changes that may emerge in pathological conditions. Noteworthy, current evidence points to an overall spared ability of combining multisensory cues, and, in particular, inputs from a damaged sensory modality with inputs from a spared modality, at least in patients with focal brain lesions (Bolognini et al., 2013a). This is likely to be the case since multiple, parallel, cortical and subcortical pathways are available for multisensory integration to occur: accordingly, if a key node of a multisensory network is damaged, alternative spared pathways may be used to re-connect the sensory systems. This allows to re-arrange sensory interactions, in order to preserve an optimal, reliable, multisensory experience. Importantly, the effects of crossmodal illusions may be even stronger in patients with brain disease than in healthy subjects, likely because neurological patients may present with sensory or motor deficits (e.g., Burin et al., 2015) that could be more vulnerable to crossmodal interferences from the intact senses. Moreover, some evidence suggests that increasing the degree of inter-sensory conflict can even enhance brain responses to crossmodal illusions (Senna et al., 2015). Many other crossmodal illusions were tested in clinical populations, though not in rehabilitation settings, including: the Ventriloquism illusion in hemianopia and neglect (Bertelson et al., 2000; Leo et al., 2008), the Aristotle's illusion in focal hand dystonia (Tinazzi et al., 2013), and the Sound-induced flash illusion in migraine (Brighina et al., 2015). They could offer novel frameworks for therapeutic developments.

References

Alais, D., Newell, F. N., and Mamassian, P. (2010). Multisensory processing in review: from physiology to behaviour. *Seeing Perceiving* 23, 3–38. doi: 10.1163/187847510X488603

Altschuler, E. L. (2005). Interaction of vision and movement via a mirror. *Perception* 34, 1153–1155. doi: 10.1068/p3409bn

Altschuler, E. L., Wisdom, S. B., Stone, L., Foster, C., Galasko, D., Llewellyn, D. M., et al. (1999). Rehabilitation of hemiparesis after stroke with a mirror. *Lancet* 353, 2035–2036. doi: 10.1016/s0140-6736(99)00920-4

Bertelson, P., Pavani, F., Ladavas, E., Vroomen, J., and de Gelder, B. (2000). Ventriloquism in patients with unilateral visual neglect. *Neuropsychologia* 38, 1634–1642. doi: 10.1016/s0028-3932(00)00067-1

Bolognini, N., Convento, S., Rossetti, A., and Merabet, L. B. (2013a). Multisensory processing after a brain damage: clues on post-injury crossmodal plasticity from neuropsychology. *Neurosci. Biobehav. Rev.* 37, 269–278. doi: 10.1016/j.neubiorev.2012.12.006

Bolognini, N., Olgiati, E., Maravita, A., Ferraro, F., and Fregni, F. (2013b). Motor and parietal cortex stimulation for phantom limb pain and sensations. *Pain* 154, 1274–1280. doi: 10.1016/j.pain.2013.03.040

Bolognini, N., Frassinetti, F., Serino, A., and Làdavas, E. (2005). "Acoustical vision" of below threshold stimuli: interaction among spatially converging audiovisual inputs. *Exp. Brain Res.* 160, 273–282. doi: 10.1007/s00221-004-2005-z

Bolognini, N., Ronchi, R., Casati, C., Fortis, P., and Vallar, G. (2014). Multisensory remission of somatoparaphrenic delusion my hand is back! *Neurol. Clin. Pract.* 4, 216–225. doi: 10.1212/cpj.0000000000000033

Bolognini, N., Spandri, V., Ferraro, F., Salmaggi, A., Molinari, A. C., Fregni, F., et al. (2015). Immediate and sustained effects of 5-day transcranial direct current stimulation of the motor cortex in phantom limb pain. *J. Pain* 16, 657–665. doi: 10.1016/j.jpain.2015.03.013

Botvinick, M., and Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature* 391:756. doi: 10.1038/35784

Brighina, F., Bolognini, N., Cosentino, G., Maccora, S., Paladino, P., Baschi, R., et al. (2015). Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions. *Neurology* 84, 2057–2061. doi: 10.1212/WNL.0000000000001584

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi: 10.1016/j.brs.2011.03.002

Burin, D., Livelli, A., Garbarini, F., Fossataro, C., Folegatti, A., Gindri, P., et al. (2015). Are movements necessary for the sense of body ownership? Evidence from the rubber hand illusion in pure hemiplegic patients. *PLoS One* 10:e0117155. doi: 10.1371/journal.pone.0117155

Cappe, C., Rouiller, E. M., and Barone, P. (2009). Multisensory anatomical pathways. *Hear. Res.* 258, 28–36. doi: 10.1016/j.heares.2009.04.017

Christ, O., and Reiner, M. (2014). Perspectives and possible applications of the rubber hand and virtual hand illusion in non-invasive rehabilitation: technological improvements and their consequences. *Neurosci. Biobehav. Rev.* 44, 33–44. doi: 10.1016/j.neubiorev.2014.02.013

Dohle, C., Kleiser, R., Seitz, R. J., and Freund, H. J. (2004). Body scheme gates visual processing. *J. Neurophysiol.* 91, 2376–2379. doi: 10.1152/jn.00929.2003

Dohle, C., Püllen, J., Nakaten, A., Küst, J., Rietz, C., and Karbe, H. (2009). Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. *Neurorehabil. Neural Repair* 23, 209–217. doi: 10.1177/1545968308324786

Driver, J., and Noesselt, T. (2008). Multisensory interplay reveals crossmodal influences on 'sensory-specific'brain regions, neural responses and judgments. *Neuron* 57, 11–23. doi: 10.1016/j.neuron.2007.12.013

Ehrsson, H. H., Rosén, B., Stockselius, A., Ragnö, C., Köhler, P., and Lundborg, G. (2008). Upper limb amputees can be induced to experience a rubber hand as their own. *Brain* 131, 3443–3452. doi: 10.1093/brain/awn297

Fink, G. R., Marshall, J. C., Halligan, P. W., Frith, C. D., Driver, J., Frackowiak, R. S., et al. (1999). The neural consequences of conflict between intention and the senses. *Brain* 122, 497–512. doi: 10.1093/brain/122.3.497

Fotopoulou, A., Jenkinson, P. M., Tsakiris, M., Haggard, P., Rudd, A., and Kopelman, M. D. (2011). Mirror-view reverses somatoparaphrenia: dissociation between first-and third-person perspectives on body ownership. *Neuropsychologia* 49, 3946–3955. doi: 10.1016/j.neuropsychologia.2011.10.011

Fotopoulou, A., Rudd, A., Holmes, P., and Kopelman, M. (2009). Self-observation reinstates motor awareness in anosognosia for hemiplegia. *Neuropsychologia* 47, 1256–1260. doi: 10.1016/j.neuropsychologia.2009.01.018

Gallagher, P., and MacLachlan, M. (1999). Psychological adjustment and coping in adults with prosthetic limbs. *Behav. Med.* 25, 117–124. doi: 10.1080/08964289909596741

Garry, M. I., Loftus, A., and Summers, J. J. (2005). Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Exp. Brain Res.* 163, 118–122. doi: 10.1007/s00221-005-2226-9

Jenkinson, P. M., Haggard, P., Ferreira, N. C., and Fotopoulou, A. (2013). Body ownership and attention in the mirror: insights from somatoparaphrenia and the rubber hand illusion. *Neuropsychologia* 51, 1453–1462. doi: 10.1016/j.neuropsychologia.2013.03.029

Kammers, M. P., Kootker, J. A., Hogendoorn, H., and Dijkerman, H. C. (2010). How many motoric body representations can we grasp? *Exp. Brain Res.* 202, 203–212. doi: 10.1007/s00221-009-2124-7

Kitadono, K., and Humphreys, G. W. (2007). Short-term effects of the 'rubber hand' illusion on aspects of visual neglect. *Neurocase* 13, 260–271. doi: 10.1080/13554790701625815

Knotkova, H., Nitsche, M. A., and Cruciani, R. A. (2013). Putative physiological mechanisms underlying tDCS analgesic effects. *Front. Hum. Neurosci.* 7:628. doi: 10.3389/fnhum.2013.00628

Lamont, K., Chin, M., and Kogan, M. (2011). Mirror box therapy-seeing is believing. *Explore (NY)* 7, 369–372. doi: 10.1016/j.explore.2011.08.002

Lefaucheur, J. P. (2013). Pain. *Handb. Clin. Neurol.* 116, 423–440. doi: 10.1016/B978-0-444-53497-2.00035-8

Lenggenhager, B., Scivoletto, G., Molinari, M., and Pazzaglia, M. (2013). Restoring tactile awareness through the rubber hand illusion in cervical spinal cord injury. *Neurorehabil. Neural Repair* 27, 704–708. doi: 10.1177/1545968313491009

Leo, F., Bolognini, N., Passamonti, C., Stein, B. E., and Làdavas, E. (2008). Cross-modal localization in hemianopia: new insights on multisensory integration. *Brain* 131, 855–865. doi: 10.1093/brain/awn003

Lotze, M., and Moseley, G. L. (2007). Role of distorted body image in pain. *Curr. Rheumatol. Rep.* 9, 488–496. doi: 10.1007/s11926-007-0079-x

Marasco, P. D., Kim, K., Colgate, J. E., Peshkin, M. A., and Kuiken, T. A. (2011). Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain* 134, 747–758. doi: 10.1093/brain/awq361

Matthys, K., Smits, M., Van der Geest, J. N., Van der Lugt, A., Seurinck, R., Stam, H. J., et al. (2009). Mirror-induced visual illusion of hand movements: a functional magnetic resonance imaging study. *Arch. Phys. Med. Rehabil.* 90, 675–681. doi: 10.1016/j.apmr.2008.09.571

Melzack, R. (1992). Phantom limbs. *Sci. Am.* 266, 120–125. doi: 10.1038/scientificamerican0492-120

Michielsen, M. E., Smits, M., Ribbers, G. M., Stam, H. J., van der Geest, J. N., Bussmann, J. B., et al. (2011a). The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke. *J. Neurol. Neurosurg. Psychiatry* 82, 393–398. doi: 10.1136/jnnp.2009.194134

Michielsen, M. E., Selles, R. W., van der Geest, J. N., Eckhardt, M., Yavuzer, G., Stam, H. J., et al. (2011b). Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabil. Neural Repair* 25, 223–233. doi: 10.1177/1545968310385127

Moseley, G. L., and Flor, H. (2012). Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabil. Neural Repair* 26, 646–652. doi: 10.1177/1545968311433209

Moseley, G. L., Gallace, A., and Spence, C. (2008). Is mirror therapy all it is cracked up to be? Current evidence and future directions. *Pain* 138, 7–10. doi: 10.1016/j.pain.2008.06.026

Nojima, I., Mima, T., Koganemaru, S., Thabit, M. N., Fukuyama, H., and Kawamata, T. (2012). Human motor plasticity induced by mirror visual feedback. *J. Neurosci.* 32, 1293–1300. doi: 10.1523/JNEUROSCI.5364-11.2012

O'Callaghan, C. (2008). Seeing what you hear: cross-modal illusions and perception. *Philos. Issues* 18, 316–338. doi: 10.1111/j.1533-6077.2008.00150.x

Ramachandran, V. S., and Altschuler, E. L. (2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain* 132, 1693–1710. doi: 10.1093/brain/awp135

Ramachandran, V. S., Rogers-Ramachandran, D., and Cobb, S. (1995). Touching the phantom limb. *Nature* 377, 489–490. doi: 10.1038/377489a0

Reinersmann, A., Landwehrt, J., Krumova, E. K., Peterburs, J., Ocklenburg, S., Güntürkün, O., et al. (2013). The rubber hand illusion in complex regional pain syndrome: preserved ability to integrate a rubber hand indicates intact multisensory integration. *Pain* 154, 1519–1527. doi: 10.1016/j.pain.2013.03.039

Romano, D., Bottini, G., and Maravita, A. (2013). Perceptual effects of the mirror box training in normal subjects. *Restor. Neurol. Neurosci.* 31, 373–386. doi: 10.3233/RNN-120273

Romano, D., Sedda, A., Dell'Aquila, R., Dalla Costa, D., Beretta, G., Maravita, A., et al. (2014). Controlling the alien hand through the mirror box. A single case study of alien hand syndrome. *Neurocase* 20, 307–316. doi: 10.1080/13554794.2013.770882

Rosén, B., Ehrsson, H. H., Antfolk, C., Cipriani, C., Sebelius, F., and Lundborg, G. (2009). Referral of sensation to an advanced humanoid robotic hand prosthesis. *Scand. J. Plast. Reconstr. Surg. Hand Surg.* 43, 260–266. doi: 10.3109/02844310903113107

Schmalzl, L., Ragnö, C., and Ehrsson, H. H. (2013). An alternative to traditional mirror therapy: illusory touch can reduce phantom pain when illusory movement does not. *Clin. J. Pain* 29, e10–e18. doi: 10.1097/AJP.0b013e3182850573

Senna, I., Russo, C., Parise, C. V., Ferrario, I., and Bolognini, N. (2015). Altered visual feedback modulates cortical excitability in a mirror-box-like paradigm. *Exp. Brain Res.* 233, 1921–1929. doi: 10.1007/s00221-015-4265-1

Snijders, H. J., Holmes, N. P., and Spence, C. (2007). Direction-dependent integration of vision and proprioception in reaching under the influence of the mirror illusion. *Neuropsychologia* 45, 496–505. doi: 10.1016/j.neuropsychologia.2006.01.003

Soler, M. D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J. M., Fregni, F., et al. (2010). Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain* 133, 2565–2677. doi: 10.1093/brain/awq184

Stein, B. E., and Meredith, M. A. (1993). *The Merging of the Senses.* Cambridge, MA: The MIT Press.

Thieme, H., Bayn, M., Wurg, M., Zange, C., Pohl, M., and Behrens, J. (2013). Mirror therapy for patients with severe arm paresis after stroke-a randomized controlled trial. *Clin. Rehabil.* 27, 314–324. doi: 10.1177/0269215512455651

Tinazzi, M., Marotta, A., Fasano, A., Bove, F., Bentivoglio, A. R., Squintani, G., et al. (2013). Aristotle's illusion reveals interdigit functional somatosensory alterations in focal hand dystonia. *Brain* 136, 782–789. doi: 10.1093/brain/aws372

Tsakiris, M., and Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *J. Exp. Psychol. Hum. Percept. Perform.* 31, 80–91. doi: 10.1037/0096-1523.31.1.80

Vallar, G., and Bolognini, N. (2014). "Unilateral spatial neglect," in *Oxford Handbook of Attention*, eds A. C. Nobre and S. Kastner (Oxford: Oxford University Press), 972–1027.

Vallar, G., and Ronchi, R. (2009). Somatoparaphrenia: a body delusion: a review of the neuropsychological literature. *Exp. Brain Res.* 192, 533–551. doi: 10.1007/s00221-008-1562-y

Wade, N., and Swanston, M. (2001). *Visual Perception: An Introduction.* Howe, UK: Psychology Press.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

CORRECTION
published: 01 March 2016
doi: 10.3389/fnbeh.2016.00033

Corrigendum: Crossmodal illusions in neurorehabilitation

*Nadia Bolognini[1,2], Cristina Russo[1] and Giuseppe Vallar[1,2]**

[1] Department of Psychology, and NeuroMi – Milan Center for Neuroscience, University of Milano-Bicocca, Milan, Italy,
[2] Laboratory of Neuropsychology, IRCCS Istituto Auxologico Italiano, Milan, Italy

Keywords: crossmodal illusions, neurorehabilitation, multisensory, body representation, pain, motor disorders, sensory disorders

A corrigendum on

Crossmodal illusions in neurorehabilitation
by Bolognini, N., Russo, C., and Vallar, G. (2015). Front. Behav. Neurosci. 9:212. doi: 10.3389/fnbeh.2015.00212

This Corrigendum is issued because the Department of Psychology, and the NeuroMi – Milan Center for Neuroscience are part of, and belong to, the same institution, namely the University of Milano-Bicocca, Milan, Italy. They are not two different institutions, as we erroneously stated in the original manuscript: that erroneous statement may affect the funding of our institutions. Accordingly, Dr. Bolognini and Dr. Vallar have 2 (not 3) affiliations: University of Milano-Bicocca, and IRCCS Istituto Auxologico Italiano, Milan, Italy. We state that the correction and the revised information do not affect the scientific validity of the results.

AUTHOR CONTRIBUTIONS

NB, CR, and GV have contributed equally to all stages of this work.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

OPEN ACCESS

Edited and reviewed by:
Katiuscia Sacco, University of Turin, Italy

****Correspondence:***
Giuseppe Vallar
giuseppe.vallar@unimib.it

Received: *04 February 2016*
Accepted: *14 February 2016*
Published: *01 March 2016*

Citation:
Bolognini N, Russo C and Vallar G (2016) Corrigendum: Crossmodal illusions in neurorehabilitation. Front. Behav. Neurosci. 10:33. doi: 10.3389/fnbeh.2016.00033

frontiers in Behavioral Neuroscience

REVIEW
published: 25 August 2015
doi: 10.3389/fnbeh.2015.00226

Assessment and rehabilitation of neglect using virtual reality: a systematic review

Elisa Pedroli[1]*, *Silvia Serino*[1], *Pietro Cipresso*[1], *Federica Pallavicini*[1] and *Giuseppe Riva*[1,2]

[1] *Applied Technology for Neuro-Psychology Lab, IRCCS Istituto Auxologico Italiano, Milan, Italy,* [2] *Department of Psycholgy, Università Cattolica del Sacro Cuore, Milan, Italy*

After experiencing a stroke in the right hemisphere, almost 50% of patients showed Unilateral Spatial Neglect (USN). In recent decades, Virtual Reality (VR) has been used as an effective tool both for the assessment and rehabilitation of USN. Indeed, this advanced technology allows post-stroke patients to interact with ecological and engaging environments similar to real ones, but in a safe and controlled way. To provide an overview of the most recent VR applications for the assessment and rehabilitation of USN, a systematic review has been carried out. Since 2010, 13 studies have proposed and tested innovative VR tools for USN. After a wide description of the selected studies, we discuss the main features of these VR tools in order to provide crucial indications for future studies, neurorehabilitation interventions, and clinical practice.

Keywords: virtual reality, USN, assessment, rehabilitation, PRISMA

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Seth Davin Norrholm, Emory University School of Medicine, USA
Tanja Nijboer, Utrecht University, Netherlands

***Correspondence:**
Elisa Pedroli, Applied Technology for Neuro-Psychology Lab, IRCCS Istituto Auxologico Italiano, Via Magnasco 2, 20149 Milan, Italy
e.pedroli@auxologico.it

Received: *19 May 2015*
Accepted: *10 August 2015*
Published: *25 August 2015*

Citation:
Pedroli E, Serino S, Cipresso P, Pallavicini F and Riva G (2015) Assessment and rehabilitation of neglect using virtual reality: a systematic review. Front. Behav. Neurosci. 9:226. doi: 10.3389/fnbeh.2015.00226

Introduction

Each year about 500,000 people suffer a stroke. Strokes are the third leading cause of death in Western countries (after cardiovascular and neoplastic diseases) and one of the leading causes of long-term severe disability (Sudlow and Warlow, 1997; Pendlebury et al., 2009; Zhang et al., 2012). Indeed, it is a catastrophic and often unexpected event with a wide range of physical and psychological consequences that involve both patients and their relatives (Wolfe, 2000; Di Carlo, 2009). Due to the debilitating initial symptoms and long-term impairment in daily life activities like locomotion and speech, the consequences of a stroke depend on type, severity, and location of the occlusion. After a stroke, it is commonly possible to identify two basic categories of impairment or disability: motor disability (including the inability to walk, problems with coordination and balance, hemiparesis, or hemiplegia) and cognitive impairments (including aphasia, memory, and visuo-spatial and executive functions impairments) (Hendricks et al., 2002; Pohjasvaara et al., 2002; Hackett et al., 2005; Langhorne et al., 2009; Lloyd-Jones et al., 2009; Sundar and Adwani, 2010). The most common cognitive impairment after a stroke, which appears in approximately 50% of patients, is Unilateral Spatial Neglect (USN) (Bowen et al., 1999; Appelros et al., 2002; Nijboer et al., 2013a). USN commonly (in 90% of cases) occurs after lesions in the right hemisphere, particularly in the parietal (inferior), temporal (superior), and/or frontal (ventral) cortex and sometimes in subcortical nuclei (Buxbaum et al., 2004). This complex syndrome can be defined as "a failure to report, respond, or orient to contralateral stimuli that is not caused by an elemental sensorimotor deficit" (Heilman et al., 1985). Patients with USN may show several symptoms in everyday life, such as eating food only on the right side of the plate, putting make-up only on the right side of their face and, forgetting to look left before crossing the street (Nijboer et al., 2013b, 2014b).

For these reasons, USN is a poor prognostic sign for both motor and cognitive rehabilitation outcomes (Buxbaum et al., 2004; Jehkonen et al., 2006; Mutai et al., 2012; Nijboer et al., 2014a).

An increasing number of theories have been proposed to explain the behaviors characteristic to USN; to date, the most interesting theories are attentional-based (Bartolomeo and Chokron, 2002; Corbetta et al., 2005; Corbetta and Shulman, 2011). Specifically, Bartolomeo said that "left neglect does not reflect an attentional deficit but an attentional bias consisting of enhanced attention to the right" (Bartolomeo and Chokron, 2002, p. 221). Indeed, Bartolomeo and Chokron argue that USN may be caused by an impairment in the exogenous (i.e., stimulus-related) orienting of attention because the endogenous (i.e., strategy-driven) way is relatively well-preserved, although it operates slowly (Bartolomeo and Chokron, 2002). In the same direction, Corbetta and colleagues (Corbetta et al., 2005; Corbetta and Shulman, 2011) argued that the attentional deficits in UNS may be mediated by a dysfunction, both functional and structural, of the two frontoparietal attention networks, in addition to damages resulting from the lesion (Corbetta et al., 2005; Corbetta and Shulman, 2011).

Paper-and-pencil tests are traditionally used to assess the presence of USN symptoms in a clinical setting. In "cancelation tasks," patients are required to find a target symbol mixed with several other distractors. The most common tests are cancelation of line (Albert, 1973), letter (Diller and Weinberg, 1976), circle (Vallar and Perani, 1986), and star (Wilson et al., 1987). However, as noted by Rengachary et al. (2009), these paper-and-pencil tests may be particularly poor at detecting USN symptoms, especially in the chronic stage (Halligan et al., 1989). Driven by attentional-based theories, it is crucial to acknowledge that patients may be able to learn a compensatory attentional strategy and, consequently, to pass a test in which they have unlimited time to identify static targets. In clinical practice, two major methods for USN rehabilitation are visual searching and stimulation techniques: the first one is meant to improve voluntary exploration of the contralesional space (Pierce and Buxbaum, 2002; Paci et al., 2010), while the second one implicitly forces the patients to explore contralesional space (i.e., prismatic adaptation or caloric, galvanic, and optokinetic stimulation) (Kerkhoff and Schenk, 2012).

None of these approaches alone is the gold standard for rehabilitation of UNS (Pierce and Buxbaum, 2002; Bowen et al., 2013); it is strictly recommended that a combination of multiple approaches be used to develop a personalized rehabilitation process (Kerkhoff and Schenk, 2012).

Computerized methods offer a promising alternative approach for USN assessment and rehabilitation (Gontkovsky et al., 2002; Pflugshaupt et al., 2004; Deouell et al., 2005; Yong Joo et al., 2010; Bonato, 2012; Rabuffetti et al., 2012; Bonato and Deouell, 2013; Smit et al., 2013; Dalmaijer et al., 2014; Vaes et al., 2015). Computerized tests are able to identify subtle deficits that a static paper-and-pencil test might miss. Moreover, the traditional methods may lack ecological validity (which is crucial for rehabilitation) (Perez-Garcia et al., 1998; Levick, 2010), and there is often no correspondence between performance at the task and performance in real life (Eslinger et al., 1992, 2004; Vriezen et al., 2001). Finally, these protocols are time-consuming and tedious both for therapists and patients because people suffering from UNS also often experience anosognosia, meaning that they are unaware of their disability.

One of the most promising solutions to improve the quality of neuropsychological assessment and rehabilitation is the use of Virtual Reality (VR). VR can make more neuropsychological practice more involving, generalizable, and ecological thanks to its ability to measure behavior in valid, safe, and controlled environments objectively and automatically; dynamic learning also may increase engagement of the patients (Rizzo et al., 2002; Brooks and Rose, 2003; Riva, 2009; Sugarman et al., 2011). First, a systematic review about the potentiality of VR for USN assessment and rehabilitation was carried out by Tsirlin et al. (2009). They underlined that VR provides an advanced human-computer interface that allows the patients to interact with, and become immersed in, a computer-generated environment similar to the real-life experience. Thanks to this advanced technology, patients can be evaluated and trained through simulations that are relevant for everyday life, eliminating the necessity to use real environments that are not always available inside a hospital. VR can also improve traditional assessment methods by providing information about head and eye movements, postural deviations, and limb kinematics, which can be useful in detecting subtle deficits. Finally, Tsirlin et al. (2009) argued that VR assessment and rehabilitation of USN could be more engaging and consequently more effective than traditional methods. Despite the incredible potential of VR for assessment and rehabilitation of USN, Tsirlin et al. (2009) noted that there are several challenges that may limit future applications in this field: the ergonomic aspects of VR systems (considering the reduced mobility of post-stroke patients), the necessary collaboration between clinicians and technicians to set up VR systems, and the costs related to the design, maintenance and use of a VR system.

Thanks to the dramatic development of VR technology, several researchers have exploited the potential of VR both for the cognitive evaluation and rehabilitation of USN. On this basis, the main goal of this systematic review is to provide an overview of the latest applications in the field of assessment and rehabilitation of USN with VR applications since 2010 to provide crucial indications for future studies and neurorehabilitation interventions. Below, we analyze the articles and describe the methodology and technology used in the articles in order to understand the developments and new perspectives.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

Search Strategy

To achieve this, a computer-based search in several databases was performed for relevant publications. Databases used for the search were: PsycINFO, Web of Science (Web of Knowledge), PubMed and Medline.

The search string was: (“Virtual Reality” OR Technolog*) AND [“Neglect” OR (“Unilateral Spatial Neglect” OR “Hemispatial Neglect” OR “Visual Neglect” OR “Visuospatial Neglect”)]. A graphical representation of the search string can been seen in **Figure 1**.

Our choice to search for both “virtual reality” and “technolog*” was to avoid missing papers due to the misleading terminologies that are often used in some studies. Acting within this strategy, we can be confident that this review is both replicable and inclusive of all possible records.

The articles were individually scanned to elaborate whether they fulfill the following inclusion criteria: (a) research article; (b) providing information about the used sample; (c) providing information about measures, and (d) published in English. These inclusion criteria were used for several reasons. As noted above, information about the sample and measures are a prerequisite.

The second search strategy (with the term Technolog*) had as a further exclusion criterion being present in the first list (already screened).

Systematic Review Flow

The flow chart of the systematic review is shown in **Figure 2** for the term “Virtual Reality” and in **Figure 3** for the term Technolog*. By searching in PsycINFO, PubMed, Medline and Web of Science (Web of Knowledge: WoK), our initial search yielded 1048 non-duplicate citations screened with “Virtual Reality” and 3892 with “Technolog*.” More details are available in the Search Strategy Table (**Table 1**). After the application of the inclusion criteria, papers were reduced to 204 and 240 articles, respectively. A deeper investigation of the full papers resulted in the exclusion of 191 and 237 articles, respectively. During the data extraction procedure, three additional full papers were excluded. In the end, 13 studies met the full criteria and were included in this review (**Table 1**). A flow diagram showing the procedure is detailed in **Figure 2** for “Virtual Reality” search strategy and in **Figure 3** for “Technolog*.”

Expert colleagues in the field were contacted for suggestions on further studies to consider in our search. Four new studies arose and have been included in the analyzed studies. To assess a risk of bias, PRISMA recommendations for systematic literature analysis have been strictly followed. Three authors (E.P., S.S., and P.C.) independently selected paper abstracts and titles and analyzed the full papers that met the inclusion criteria, resolving disagreements through consensus.

Results

In the current systematic review, we aim to provide a review of state-of-the-art experimental studies (from 2010 to 2014) focused on the use of VR for the assessment and rehabilitation of USN. In total, 12 studies met the inclusion criteria, were critically reviewed, and are summarized in **Table 2**.

In the following paragraphs, we critically reviewed the selected studies by dividing them according to the main purposes of the virtual tools proposed: (1) neuropsychological assessment of USN symptoms; (2) neuropsychological rehabilitation of USN symptoms; and (3) comprehensive platform for both assessment and rehabilitation of USN symptoms.

The Application of VR in the Assessment of USN

As it was described in the introduction, USN is typically evaluated by paper-and-pencil tests despite the aforementioned limitations of these tools. In this section, to deeply review the potential of VR for improving and/or integrating the traditional evaluations

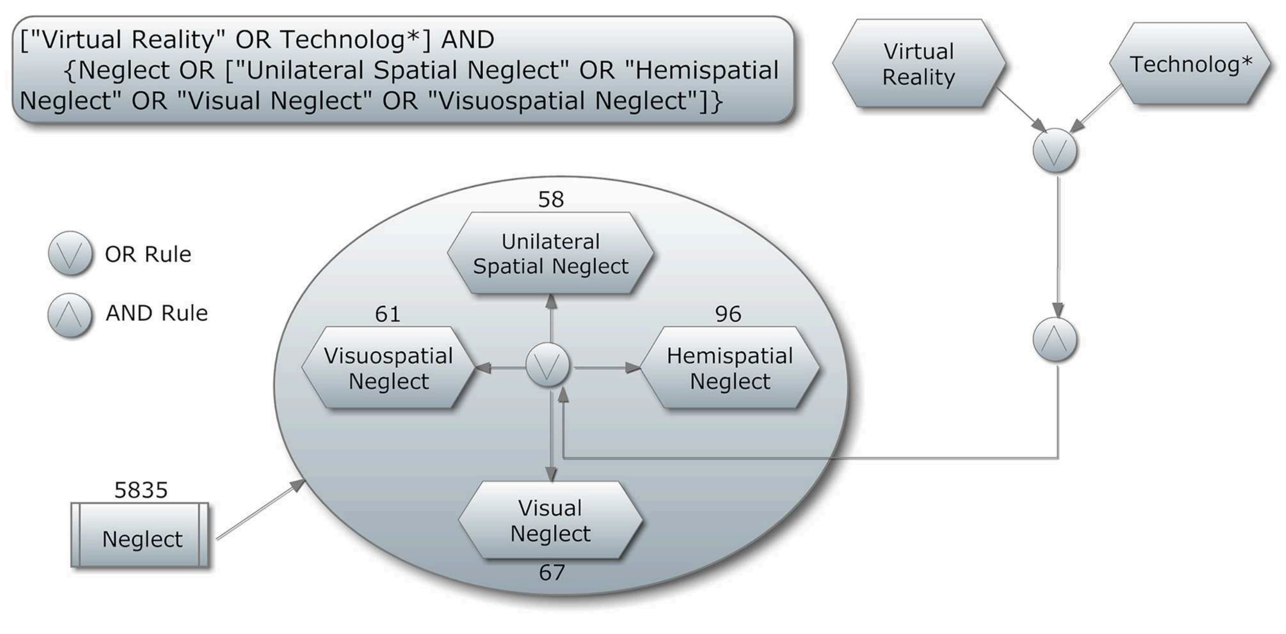


FIGURE 1 | Search strategy. A graphical representation.

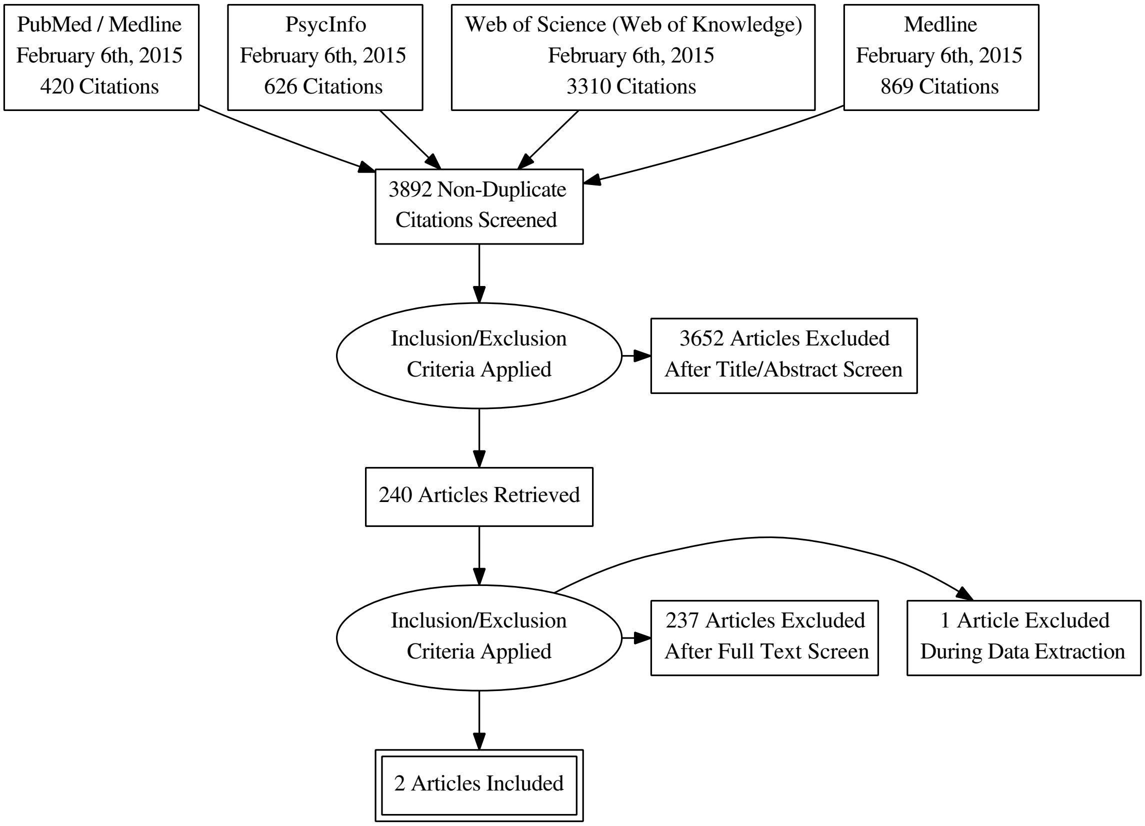


FIGURE 2 | Search strategy using "Virtual Reality" term.

of USN, we analyzed the selected articles to provide an overview of the most recent virtual diagnostic tasks.

The first article analyzed was written by Kim et al. (2010), who used a 3D immersive VR program for street-crossing to assess USN in post-stroke patients. They assessed 32 patients, 16 with USN and 16 without USN. USN was assess by physiatrists and occupational therapists. They observe patients in the real life situations in order to find evidence of USN.

Patients was assesses during one session both with virtual and paper-and-pencil test. The test used are the Line Bisection Test (Schenkenberg et al., 1980) and the Line Cancellation Test (Albert, 1973).

At the beginning of virtual task, the patient see an avatar in front of a traffic light, the mission is cross the street without accident. If a car approaching to the avatar, patient have to push a stop button in order to avoid an accident. If patients failed to recognize the car approaching, they had visual and auditory cues to stop the avatar before failing their mission.

The results demonstrated that the two groups (patients with USN vs. patients without USN) showed differences in several variables analyzed during the task: deviation angle, left-to-right reaction time ratio, left visual, auditory cue rates, and left failure rate. Kim et al. (2010) showed that USN can be detected and measured easily and safely using their VR test. The authors also compared these virtual tools to the paper-and-pencil tests and found one correlation: the Line Bisection Test (Schenkenberg et al., 1980) correlated significantly with the deviation angle in the USN group.

In a similar test developed by Mesa-Gresa et al. (2011), they used a conventional LCD monitor, a surround system, a navigation and interaction joystick, and an optical tracking system (TRACKIR). Head movements were detected thanks to a cap with three reflecting markers and a USB infrared camera. A sample of 25 patients was analyzed, divided into neglect patients ($n = 5$) and non-neglect patients ($n = 20$) according to results obtained at the following tests: Behavioral Inattention Test (BIT), Color Trail Making Test (CTT), and Conners' Continuous Performance Test-II (CPT-II) (Peña-Casanova et al., 2006).

They planned a training session before the task that consisted of crossing a two-way road twice to arrive at a supermarket and then return. The task ended when patients went to and came back from the supermarket twice, making a maximum of four collisions with a car. They evaluated the following: how many times the participants looked to the left and to the right, the total time needed, the total number of accidents, whether the task was successfully accomplished, and a neuropsychological battery. During the VRSCT, negligent subjects showed a higher number of collision with a car than the other group, indeed indicating that the tool was able to discriminate between the two groups in clinical practice.

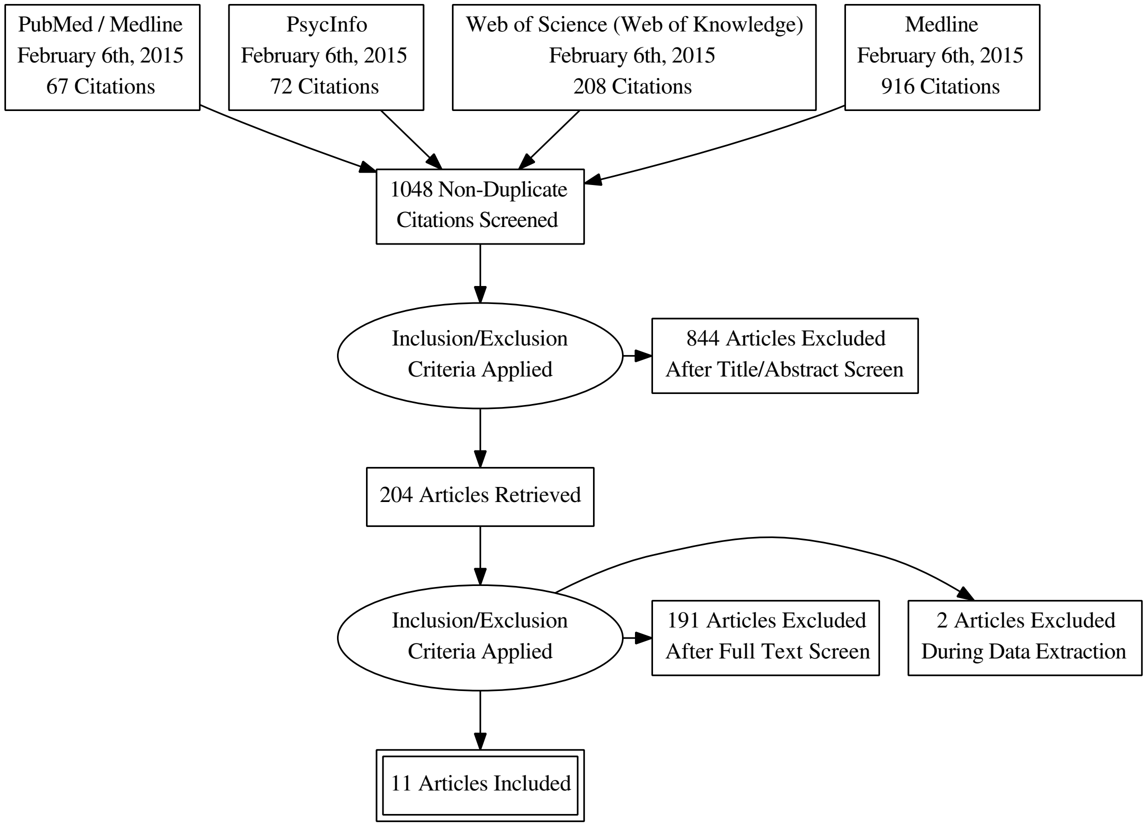


FIGURE 3 | Search strategy using "Technolog*" term.

Peskine et al. (2011) developed a task that took place in a virtual city: patients have to count the number of bus stops they see. The sample included nine patients with a history of right cerebrovascular accidents (five of whom had visuospatial USN) and matched controls both for age and sex. USN was assessed using the Bells Cancellation Test (Gauthier et al., 1989) and the Catherine Bergego Scale (CBS; Azouvi et al., 2006). Patients used an HMD with an electromagnetic sensor system able to detect movements and sat on a swivel chair to turn on their own vertical axis. They had to move in the city, locate the swings in a park, and count all the bus stops; the examiner noted the patient's progress. The virtual assessment was done in just one session. Results showed that patients omitted more targets than controls and, most importantly, four patients without USN during the cancelation test showed USN in the virtual task.

Another navigation task was developed by Buxbaum et al. (2012). They created a "Virtual Reality Lateralized Attention Test" (VRLAT), a computerized measure of USN. They compared 71 USN patients with 10 control subjects. For the clinical assessment Buxbaum et al. (2012) used: a modified version of Bell Cancellation Test (Gauthier et al., 1989), the Letter Cancellation and Line Bisection Tests (Wilson et al., 1987), a modified version of the "fluff" test (Cocchini et al., 2001), a laser line-bisection task (Buxbaum et al., 2004), and a modified version of the Moss Real World Navigation (RWN) test (Buxbaum et al., 2008). During the VRLAT patient had to name all stationary objects in the scene while following a virtual winding path (i.e., navigation can be executed sometimes by the participants and sometimes by the experimenter). The program included three array conditions (i.e., simple, complex, and enhanced), and all patients completed all levels twice, once "coming" and once "going." The software ran on a personal computer with a flat-screen video display; patients used a Logitech Attack 3 joystick.

This test seems to be better than traditional tests at predicting performance in real world. For this reason the VRLAT is a good tool for the assessment of USN. It's quick and easy to use, doesn't require specialized equipment, and could be useful both in clinical settings and in rehabilitation.

Aravind and colleagues (Aravind and Lamontagne, 2014; Aravind et al., 2015) developed a navigation task in a virtual room divided into three sub-tasks and analyzed the performance of 12 patients. A diagnosis of USN was based on the motor free visual perceptual test (MVPT; Colarusso and Hammill, 1972), and/or the Star Cancellation Test (Wilson et al., 1987). Clinical assessment included: Bells Cancellation Test (Gauthier et al., 1989), Line Bisection Tests (Wilson et al., 1987), the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005), and the Trail Making Test-B (Army Individual Test Battery, 1944). Two of these tasks ("obstacle detection task" and the "joystick-driven obstacle avoidance task") were analyzed in the first

TABLE 1 | Search strategy results.

"Virtual Reality" and	"Neglect"	"Unilateral spatial neglect"	"Hemispatial neglect"	"Visual neglect"	"Visuospatial neglect"	Other source	Total
PsycINFO	52	5	7	4	4		72
Web of Science (Web of Knowledge)	112	18	35	25	18		208
PubMed	42	7	9	4	5		67
Medline	881	7	14	8	6		916
TOTAL	1087	37	65	41	33	12	1275
Non duplicated	911	13	57	31	24	12	1048
Excluded (after reading Title and Abstract)							844
Retrieved							204
Excluded (after applying inclusion criteria)							191
Excluded (missing experimental data)							2
Included							11
Technolog* and	**"Neglect"**	**"Unilateral Spatial Neglect"**	**"Hemispatial Neglect"**	**"Visual Neglect"**	**"Visuospatial Neglect"**	**Other source**	**Total**
PsycINFO	591	7	11	12	5		626
Web of Science (Web of Knowledge)	3281	6	11	6	6		3310
PubMed	396	7	6	8	3		420
Medline	838	4	5	3	19		869
TOTAL	5106	24	33	29	33	12	5237
Non duplicated	3813	11	17	14	25	12	3892
Excluded (after reading Title and Abstract)							3652
Retrieved							240
Excluded (after applying inclusion criteria)							237
Excluded (missing experimental data)							1
Included							2

selected paper (Aravind et al., 2015); the other task, "locomotor obstacle avoidance task," was described in another publication (Aravind and Lamontagne, 2014). Patients wearing a Visor SX60 head-mounted display (HMD) (NVIS, USA) and had a joystick (Attack3, Logitech, USA) to interact with the environment.

In the "locomotor obstacle avoidance task" (Aravind and Lamontagne, 2014) patient had to walking toward a target and avoid a collision with an moving object. The moving obstacle may approaching from center, right, or left.

During the "obstacle detection task" (Aravind et al., 2015) the patient was seated at a table with a joystick in the non-paretic hand. One of the three objects placed in center, right or left in the other side of the virtual room may approach toward the patient. When patient perceived the object had to push the button.

During the "joystick-driven obstacle avoidance task" (Aravind et al., 2015) the patient is passively moved toward a target and must avoid objects that move at him. The patient may avoid the object moving to the right or left or up or slow down the speed of movement with the joystick.

In the first task, patients detected contralesional obstacles at closer proximities compared to ipsilesional ones. For the "joystick-driven obstacle avoidance task," participants begin to avoid objects at the last moment before the collision. Instead, they found that the performances on these paper-and-pencil tests were negatively associated with distances at detection, but the association lost significance with the exclusion of one patient (an outlier). For the "locomotor obstacle avoidance task," Aravind and colleagues (Aravind and Lamontagne, 2014; Aravind et al., 2015) showed that 8 out of 12 subjects collided with either contralesional or head-on obstacles or both. Delay in detection and execution of avoidance strategies and smaller distances from obstacles were observed for colliders subjects compared to non-colliders one. After analyzing all three tasks, Aravind and colleagues (Aravind and Lamontagne, 2014; Aravind et al., 2015) argued that their system showed a typical pattern for USN patients and thus can be used for assessment.

The last article in this section is that of Fordell et al. (2011). They designed a VR Diagnostic Test Battery (VR-DiSTRO). The battery included the virtual version of four classical sub-tests: Star Cancellation and Line Bisection Test (Wilson et al., 1987), Visual Extinction Test (Geeraerts et al., 2005), and Baking Tray Task (Tham, 1996). During the experiment, patients have to

TABLE 2 | Studies which met the inclusion criteria.

References	Characteristics of sample	Characteristics of VR applications	Sessions	Main outcomes
THE APPLICATION OF VR IN THE ASSESSMENT				
Kim et al., 2010	Thirty-two post-stroke patients divided into two groups: .with USN (*n* = 16: 6 female, 10 male; mean age = 52.9, SD = 16.8; mean onset (months) = 3.9, SD = 3.2), .without USN (*n* = 16: 5 female, 11 male; mean age = 60.1, SD = 12.1; mean onset (days) = 2.2, SD = 1.7)	3D immersive VR program for street crossing. Patients had 16 missions: four missions at four different velocities. If patients failed to recognize the car approaching, they had visual and auditory cues to stop the avatar before failing their mission	Patients completed the two conventional neuropsychological paper-and-pencil tests (Line Cancellation Test and Line Bisection Test) on the same day they completed the 3D virtual street assessment	Deviation angle, left-to-right reaction time ratio, left visual auditory cue rates and left failure rate in the VR program showed significant differences between the two groups. Depending on the direction of approach of the virtual car, the left parameters were significantly higher than the right parameters in the USN group. Risky behavioral aspects in unilateral neglect patients can be safely detected using this program
Mesa-Gresa et al., 2011	Twenty-five post-stroke patients: 11 female, 14 male; mean age = 51.2, SD = 12.6; mean onset (days) = 504.4, SD = 335.1	The VRSCT (VR Street Crossing Test): during the training session, patients did a single task without traffic or other distractors. In the assessment session, the task consisted of twice crossing a two-way road to arrive at a supermarket and return. The task ended when patients went to and came back from the supermarket twice, making a maximum of four accidents	The cognitive assessment (BIT, CT ad CPT-II) was conducted during the same week as the virtual training. The training session took approximately 10 min and the evaluation session lasted until the patient finished the task and/or the patient was considered to have failed the task	Validity of VRSCT for the assessment of both negligent and non-negligent ABI patients VRSCT system correlated with BIT score for non-negligent patients. Negligent patients show more accidents than other patients. Also assessed the appropriate emotional response
Peskine et al., 2011	Nine post-stroke patients: 5 with USN and 4 without USN (4 female, 5 male; mean age = 50, SD = 15; mean onset (months) = 16.1, SD = 30.2. Nine control participants: 4 female, 5 male; mean age = 50.6, SD = 16.1;	Patients had to move in the city, locate a main target (swings in a park), and count all the bus stops. The town had 13 bus stops, six on one side and seven on the other side of the street	Neglect was assessed with the Bell test and the CBS. All subjects and controls received one session of virtual navigation	The main finding is that four patients who did not display USN on the cancelation task test, or in some cases on the behavioral scale, showed neglect symptoms on the virtual task
Buxbaum et al., 2012	Seventy post-stroke patients: 31 female, 39 male; mean age = 59.5, SD = 10.6; mean onset (months) = 29, SD = 23.7, 10 control participants: 5 female, 5 male; mean age = 62.2, SD = 15.1;	The VRLAT requires participants to travel along a virtual, non-branching path, either propelling themselves using a computer joystick (participant condition) or passively viewing the environment while an examiner navigates the path at a constant rate (examiner condition). Participants were asked to identify virtual objects on either side of the path and to avoid colliding with the objects	All participants completed a testing protocol (VRLAT and a real-world navigation task, tests of sensory and motor function, modified Bell Cancellation Test, Letter Cancellation and Line Bisection Tests, modified Fluff Test, laser Line-Bisection Task, and RWN) in approximately 90 min	The VRLAT demonstrated strong sensitivity and specificity, minimal practice effects, and strong validity, and outperformed traditional paper-and-pencil tests in the prediction of real-world collisions
Aravind and Lamontagne, 2014	Twelve post-stroke participants with USN: 8 female, 4 male; mean age = 60.7, SD = 8.6; mean onset (months) = 13.5, SD = 24.3	VR environment consisted of a room with a blue circular target on the wall at the far end and three red cylinders (the obstacles). In the locomotor obstacle avoidance task patient had to walking toward a target and avoid a collision with an moving object	The locomotor obstacle avoidance task, the tests for the diagnosis of USN (MVPT, and Star Cancellation), the clinical assessment (Bells Test, Line Bisection Tests, MOCA, and Trail Making Test-B), and hand dominance were administered on 2 separate days within 1 week	8 out of 12 participants collided with either contralesional or head-on obstacles or both. Delay in detection (perceptuo-motor task) and execution of avoidance strategies, and smaller distances from obstacles (locomotor task), were observed for colliders compared to non-colliders

(Continued)

TABLE 2 | Continued

References	Characteristics of sample	Characteristics of VR applications	Sessions	Main outcomes
Aravind et al., 2015	Twelve post-stroke participants with USN: 8 female, 4 male; mean age = 60.7, SD = 8.6; mean onset (months) = 13.5, SD = 24.3	VR environment consisted of a room with a blue circular target on the wall at the far end and three red cylinders, the obstacles. During the “obstacle detection task” one object approaching to the patients from the center, right or the left side of the room. When patient perceived the object had to push the button. During the “joystick-driven obstacle avoidance task” the patient is passively moved toward a target and must avoid objects that move at him. The patient may avoid the object moving to the right or left or up or slow down the speed of movement with the joystick	The obstacle detection task, joystick-driven obstacle avoidance task, the tests for the diagnosis of USN (MVPT, and Star Cancellation), the clinical assessment (Bells Test, Line Bisection Tests, MOCA, and Trail Making Test-B), and hand dominance were administered on 2 separate days within 1 week	In the detection task, the contralesional and head-on obstacles were detected at closer proximities compared to the ipsilesional obstacle. For the avoidance task, collisions were observed only for the contralesional and head-on obstacle approaches. For the contralesional obstacle approach, participants initiated their avoidance strategies at smaller distances from the obstacle and maintained smaller minimum distances from the obstacles. The distance at detection showed a negative association with the distance at the onset of avoidance strategy for all three obstacle approaches
Fordell et al., 2011	Thirty-one post-stroke patients divided into two groups:.with USN (*n* = 9: 3 female, 6 male; mean age = 73.3, SD = 12; mean onset = 2 weeks), .without USN (*n* = 22: 6 female, 16 male; mean age = 74.4, SD = 10.8; mean onset = 2 weeks)	VR-DiSTRO: virtual star cancelation, line bisection, visual extinction, Baking tray task. The patients used a robotic pen and shutter glasses for stereoscopic vision	The virtual and the classic versions of the test were administered with no time limits. Mean assessment time was 15 min for the VR-DiSTRO	VR-DiSTRO total score showed a 100% sensitivity and 82% specificity in accurately identifying USN patients
THE APPLICATION OF VR IN THE REHABILITATION				
Kim et al., 2011	Twenty-four post-stroke patients with USN divided into two groups: virtual reality (VR) group (*n* = 12: 3 female, 9 male; mean age = 62.3, SD = 10.2; mean onset (months) = 22.8, SD = 7.6) and the control group (*n* = 12: 7 female, 5 male, mean age = 67.2, SD = 13.9; mean onset (months) = 25.5, SD = 18.5)	The VR group received VR training with a system equipped with a monitor, a video camera and computer-recognizing gloves. There are three tasks: “Bird and Ball” (i.e., they had to touch a flying ball to turn it into a bird), “Coconut” (i.e., they had to catch coconuts falling from a tree) and “Container” (i.e., they had to move a box from one side to another). The control group received conventional neglect therapy such as visual scanning training	30 min a day, 5 days per week for 3 weeks. Both groups were assessed, before and after the training, with: Star Cancellation Test and the Line Bisection Test, CBS, and K-MBI	The changes in star cancelation test results and CBS in the VR group were significantly higher than those of the control group after treatment
Navarro et al., 2013	Thirty-two post-stroke patients divided into three groups:.with USN (*n* = 17: 5 female, 12 male; mean age = 58.5, SD = 10.1; mean onset (days) = 322.6, SD = 243.9), .without USN (*n* = 15: 7 female, 8 male; mean age = 50.8, SD = 13.5; mean onset (days) = 482.9, SD = 216.8). control group (*n* = 15: 3 female, 12 male; mean age = 54.6, SD = 5.7)	The VRSCT (VR Street Crossing Test): during the training session, patients did a single task without traffic or other distractors. In the assessment session, the task consisted of twice crossing a two-way road to arrive at a supermarket and return. The task ended when patients went to and came back from the supermarket twice, making a maximum of four accidents	One session divided into two parts: training (patients became acclimated to the hardware and software) and assessment (two consecutive repetitions of virtual street crossing). The neuropsychological assessment (BIT, CPT-II, Stroop Test, Color Trail Test, BADS—Zoo Map Test and Key Search Test) was made 3 days before or after the VR session	Patients with USN have a lack of efficacy in the task. That is, stroke subjects with USN received poorer results (higher values) than patients without USN, and stroke subjects as a whole received poorer results than healthy subjects

(Continued)

TABLE 2 | Continued

References	Characteristics of sample	Characteristics of VR applications	Sessions	Main outcomes
Mainetti et al., 2013	One right-hemisphere stroke patient with USN: Male, 65 years old, right fronto-temporal intraparenchymal hemorrhagic lesion in 2009	The "Duckneglect" platform, which included specially-designed games that require patients to reach targets with an increasing level of difficulties and visual and auditory cues	The rehabilitation lasted for half an hour each day, 5 days a week, for 1 month. with a follow-up 5 months later. A complete neuropsychological assessment (Line Cancellation Test, Letter Cancellation Test, Line Bisection Test, MMSE, Attentional Matrices and the Token Test).was done before, after and 5 months later the training	Significant improvement in the follow-up test, and a generalization to everyday life activities
van Kessel et al., 2013	Twenty-nine post-stroke patients divided into two groups:.control (n = 15: 5 female, 10 male; mean age = 59.1, SD = 6.8; mean onset (days) = 157.6, SD = 117.2), .experimental (n = 14: 7 female, 7 male; mean age = 61.8, SD = 7.8; mean onset (days) = 140.6, SD = 133.6)	New computerized training based on the "Visual Scanning Training" (TSVS) + Driving simulator tasks: in the first, they have to maintain their position in the middle of a street while an car moved at 50 km/h (Line Tracking Task); in the second, patients were asked to select a large rectangular dot target overlapping with the driving scene (Single Detection Task—CVRT); the third one was the combination of the previous two tasks	All patients received 30 training sessions (5 days a week, 1 h each day, for 6 weeks). A neuropsychological assessment (Line Cancellation Test, Letter Cancellation Test, Line Bisection Test, Bells Test, Word Reading Task, Gray Scales, and Baking Tray Task).was done before and after the training	No significant group and interaction effects were found that might reflect additional positive effects of dual task training
INTEGRATED PLATFORMS				
Tanaka et al., 2010	Two right-hemisphere stroke patients with USN: Patient A (female, 78 years old, parietal and temporal lobe infarction, onset 1 week) and Patient B (male, 62 years old, infarction in the middle cerebral artery territory, onset 49 weeks)	Using a head-mounted display (HDM), they administered different versions of the Line Cancellation Test: zoomed, normal or reduced, object-centered or with egocentric coordinates, with or without arrows	One session. Also the paper-and-pencil version of the Line Cancellation Test was administrated	The assessment of USN using an HMD system may clarify the left neglect area, which cannot be easily observed in the clinical evaluation for USN
Sugarman et al., 2011	One right-hemisphere stroke patient with USN: Female, 66-year old, massive right hemisphere stroke, onset 15 months	SeeMe system. Participants stood in a specific area in front of a large monitor that displayed the virtual scenes, seeing herself on the screen in real time, and being able to use trunk and limb movements to interact with the virtual environment	8 weekly 1-h treatment sessions using the SeeMe system. Three of the SeeMe tasks/games were used for treatment and a fourth task was used for evaluation. She was assessed on the first and last days of treatment	The right hippocampus plays a critical role in allocentric navigation, particularly when cognitive impairment is present

do both virtual and classic versions of the test. The patients used a robotic pen (Phantom Omni haptic device) and shutter glasses for stereoscopic vision. All virtual tests took 15 min. The sample was composed of 31 post-stroke patients: 12 had a left-sided lesion and 19 had a right-sided one. VR-DiSTRO correctly identified the USN patients in the group, showing a 100% sensitivity and 82% specificity to correctly identify USN in the sample. Additionally, 77% of the sample said that the system was easy to use. The agreement with paper-and-pencil tests was moderate to almost perfect, indicating that this virtual battery was able to detect USN at least as well as the classic tests.

The Application of VR in the Rehabilitation of USN

In order to investigate the potential of VR in USN rehabilitation, we provided an overview of the most recent studies showing different and alternative solutions compared with the traditional methods of rehabilitation. First of all, neuropsychological rehabilitation of USN must take into account the specific needs of each patient. For this reason, a more customizable neuropsychological application is essential.

The traditional rehabilitation methods are often characterized by repetitive exercises, non-consideration of the individual patients' differences and needs, and the inability to generalize the performance and outcomes as not measured and quantified.

For instance, the prisms technique, one of the most effective techniques in the neuropsychological rehabilitation of USN, induces an optical shift of the visual field to the right; the patients have an adaptation to this visual distortion that reduces neglect symptoms (Rossetti et al., 1998; Jacquin-Courtois et al., 2013; Leigh et al., 2015). Between the various techniques it is the most effective one, but not yet to be widely used in clinical practice. For this reason there is a need for innovative rehabilitations methods able to decrease USN behavior for long-term.

Kim et al. (2011) examined 24 stroke patients with USN divided into two groups. The VR group ($n = 12$) received a VR training with a system equipped with a monitor, a video camera, and computer-recognizing gloves. Patients had to complete three tasks: "Bird and Ball" (i.e., they had to touch a flying ball to turn it into a bird), "Coconut" (i.e., they had to catch coconuts falling from a tree), and "Container" (i.e., they had to move a box from one side to another). The control group ($n = 12$) received conventional USN therapy such as reading, visual tracking, writing, drawing and copying, and puzzles. Both groups had daily sessions of 30 min day, five sessions per week for 3 weeks. Both groups were assessed with conventional USN tests such as: the Star Cancellation Test and the Line Bisection Test (Wilson et al., 1987), the CBS (Azouvi et al., 2003) and the Korean version of the Modified Bartel Index (K-MBI; Jung et al., 2007). Results showed that only the VR group improved in the Star Cancellation Test (Wilson et al., 1987) and in the CBS (Azouvi et al., 2003) after the rehabilitation period.

Navarro et al. (2013) assessed the clinical validation, usability, and convergent validity of the "Virtual Street Crossing System" (Mesa-Gresa et al., 2011) to find out if it could be used for rehabilitation of USN. Their sample was composed of 17 USN patients, 15 non-USN patients and 15 control subjects. The rehabilitation task was the same used by Mesa-Gresa and colleagues in their study (Mesa-Gresa et al., 2011) and described previously. After the virtual task patients were administered a modified version of the Short Feedback Questionnaire (SFQm; Witmer and Singer, 1998). Patients were also assessed with some neuropsychological tests like: BIT, CPT-II, Stroop Test, Color Trail Test, BADS—Zoo Map Test, and Key Search Test (Peña-Casanova et al., 2006). The assessment was administered 3 days before or after the VR session. Patients with USN showed a lack of efficacy in the task, for example, they made more accidents than other groups. The results of their study showed the clinical effectiveness of the street-crossing system as confirmed by the VR outcomes, and the correlation with the scores of the neuropsychological tests.

The "Duckneglect" platform was developed by Mainetti et al. (2013). They analyzed a single case in order to check the improvement in USN using their system for rehabilitation. The patient, IB, was a 65-year-old male with a right fronto-temporal intraparenchymal hemorrhagic lesion that occurred in 2009; he's right-handed and has had 18 years of education. This system included specially-designed games requiring patients to reach some targets through different levels of difficulty using visual and auditory cues. A webcam, connected to the host PC, was positioned frontally to the patient's face, and two loud speakers were positioned near the patient to create a spatialized sound. Video of the patient was acquired from the camera and real-time processed to extract his silhouette from the background. The silhouette was then pasted onto the virtual scene of the rehabilitation task. In the end, the final scene was displayed on a screen in front of the patient. Before and after rehabilitation training a fully neuropsychological battery was administered: Line Cancellation Test (Albert, 1973), Letter Cancellation Test (Diller and Weinberg, 1976), Line Bisection Test (Schenkenberg et al., 1980), the Mini Mental State Examination (MMSE; Folstein et al., 1983), the Attentional Matrices (Spinnler and Tognoni, 1987), and the Token Test (DE RENZI and Vignolo, 1962). The rehabilitation lasted for half an hour every day, 5 days a week for 1 month. 5 months later, the patient came back for a follow-up and exhibited a significant improvement both on a classic paper-and-pencil test and other neuropsychological tasks. The improvement was also present for activities of daily living.

van Kessel et al. (2013) analyzed the performance of 29 post-stroke (right hemisphere) patients during their rehabilitation with a new computerized training method based on the "Visual Scanning Training" (TSVS) of Pizzamiglio (Pizzamiglio, 1990). Patients were divided into two groups: the experimental group ($n = 14$) received the computerized training while control group ($n = 15$) received traditional training. All patients received 30 training sessions 5 days a week for 6 weeks, 1 h per day. They used several tests for pre- and post-training assessment: paper-and-pencil tests, observation scales and the Driving Simulator Tasks. The paper-and-pencil tests are: Line Cancellation Test (Albert, 1973), Letter Cancellation Test (Diller and Weinberg, 1976), Bells Cancellation Test (Gauthier et al., 1989), Line Bisection Test (Schenkenberg et al., 1980), Word Reading Task (Làdavas et al., 1997), Gray Scales (Tant et al., 2002), and Baking Tray Task (Tham and Tegnér, 1996). The observation scales include: Semi-structured scale for the evaluation of personal and extrapersonal neglect (Zoccolotti et al., 1992), and Subjective Neglect Questionnaire (Towle and Lincoln, 1991). In the Driving Simulator Tasks, patients had to perform three tasks: Line Tracking Task, Single Detection Task (CVRT), and a combination of the previous two tasks. During the training sessions, the TSVS was composed of the following exercises: Large Screen Digit Detection, copying lines drawn on a dot matrix, reading and copying training and figure description. During the first and third weeks, both groups received the same treatment: on Monday and on Wednesday they did the TSVS tasks and on Thursday and Friday they did the TSVS and the lane tracking. During the second and fourth weeks, patients worked for just 2 days: the experimental group did the TSVS and the dual task while the control group did the TSVS and the lane tracking. van Kessel et al. (2013) didn't find any significant group or interaction effects that might underline additional positive effects of the dual task training; they weren't the result of other factors like spontaneous recovery or learning effects.

The Application of Integrated Platform for USN

Two of the selected studies proposed integrated VR platforms that are useful both for assessment and rehabilitation of USN.

An interesting example was given by Tanaka et al. (2010), who developed an HMD for the assessment and rehabilitation of USN.

They tested two post-stroke patients with USN using a combined system (Charge-Coupled Device camera, HMD, and a computer) programmed to show in the display a modified version of the classic Line Cancellation Test (Albert, 1973). They administered the standard paper-and-pencil task and six modified versions task created by manipulating the zoom (in or out), the coordinates of visual field (object-centered and egocentric), and the presence of cue (arrows). These manipulations have been made in order to find and identify the left neglect area. The study confirmed that, thanks to the special assessment through HDM, it was easier to identify the neglected area of the patients. These results might provide a more precise assessment and a more focused rehabilitation. Tanaka et al. (2010) showed that, with a reduced image condition and the arrows condition, performance at the cancelation task improved.

The other article was a feasibility study by Sugarman et al. (2011) proposing new tools that could be used both for assessment and rehabilitation: SeeMe. The system was tested on a single USN patient (66 years old) who had a right hemisphere stroke 15 months previously. The woman was invited to use the tool for 1 h each day for 8 weeks. The patient stood in a specific area in front of a large monitor that displayed the virtual scenes, seeing himself on the screen in real time and being able to use trunk and limb movements to interact with the virtual environment. A single screen-mounted camera and a vision-based tracking system captured and converted the user's movements. Three tasks were used for the rehabilitation and four for the assessment (i.e., React task, the patient have to touch the virtual balls that appear randomly on both sides of the screen). The patient was assessed on the first and on the last day of the treatment with SeeMe and with the standard paper-and-pencil tests. Also the SFQ (Witmer and Singer, 1998) an open ended interview was administered on the last day of treatment. To the SFQ (Witmer and Singer, 1998) patient assigns 5 points out of 5 in almost every question except the one that assesses whether the virtual environment looks real. To this question the patient assigns a score of 2 out of 5. For the assessment task results indicated a difference between movement times (defined as "the time elapsed between the appearance of the target and the subject's virtual contact with the target") in the right and the left space. Moreover, after training there was an improvement in movement times for the neglected space and in the paper-and-pencil test for USN.

Conclusions

The aim of this review is to describe and to critically analyze the most recent virtual tools developed and tested for the assessment and rehabilitation of USN in order to provide crucial indications for future studies, neurorehabilitation interventions, and clinical practice.

To date, traditional paper-and-pencil methods are still the most widely used technique in the clinical practice, despite several concerns both for assessment and rehabilitation of USN symptoms.

Regarding the assessment, the traditional paper-and-pencil tests may be deficient in detecting USN symptoms in the chronic stage of the disease (Rengachary et al., 2009), and their sensitivity and specificity varies between 38 and 52% (Agrell et al., 1997; Lindell et al., 2007; Fordell et al., 2011). On the other hand, regarding rehabilitative interventions, there is the prisms' technique, which is one of the most effective, but not the most used, techniques in neuropsychological rehabilitation of USN. It typically consists of sessions of repetitive exercises that have to be done several times a week but, unfortunately, have a limited effect in time (Rossetti et al., 1998; Newport and Schenk, 2012).

It is possible to note that paper-and-pencil tools use static, two-dimensional, and geometrical targets, which are far from those of a real, or virtual, environment. These tasks generally require a simple visual search in the near space, allowing only the diagnosis of peripersonal USN (Robertson and Halligan, 1999; Deouell et al., 2005; Kim et al., 2010; Aravind and Lamontagne, 2014). Otherwise, a real environment requires dynamic responses to the relevant stimuli that, in personal and extrapersonal space, change every time (Deouell et al., 2005; Buxbaum et al., 2008; Kim et al., 2010). This is a crucial feature of virtual environments since personal and extrapersonal USN are two subtypes of this syndrome that can be dissociated (Robertson and Halligan, 1999; Halligan et al., 2003). Specifically for rehabilitation, the use of moving stimuli may be crucial to modulate patients' visual attention; these kinds of objects can capture and drive attention to the left side of the space. Indeed, some recent evidence has reported that a moving cue in the left side of a task's space improved target detection in that area (Butter et al., 1990; Mattingley et al., 1994; Tanaka et al., 2010).

Moreover, both for static and moving stimuli there were different gradients of increasing reaction times, with a progression from the ipsilesional field toward the midline and into the contralesional field (Smania et al., 1998; Deouell et al., 2005; Dvorkin et al., 2007). Because of this feature, the computer version of reaction time tasks was generally more sensitive than paper-and-pencil tests (Rengachary et al., 2009; Bonato et al., 2012). One of the reasons for this behavioral pattern could be the predisposition of the patient with USN to initiating visual scanning of the environment from the ipsilesional side (Smania et al., 1998; Dvorkin et al., 2007; Aravind and Lamontagne, 2014; Aravind et al., 2015).

VR technologies offer impressive opportunities both for the rehabilitation and assessment of different cognitive deficits, including USN (Schultheis and Rizzo, 2001; Riva et al., 2004; Bohil et al., 2011).

According to the results of this systematic review, VR seems a promising instruments both for the assessment and rehabilitation of USN.

However, the trade-off between the incredible progress of VR and the need of methodological rigor and the possibility to the apply experimental protocols in the clinical practice has still to cope with different challenges.

First, as mentioned previously, Tsirlin and colleagues in their review (Tsirlin et al., 2009) underlined some characteristics of VR technologies that should be taken into consideration for future VR applications in this field.

The most important one is the ergonomic aspect of VR tools. Patients have specific needs to be considered, especially post-stroke patients who typically have to use a wheelchair for locomotion (Tsirlin et al., 2009). Our analysis showed that most of the selected studies have proposed VR assessment tools with greater attention paid to the ergonomic aspect in order to meet the needs of patients. In particular, it emerged that most of the recent VR systems could possibly be used with a chair or a wheelchair. Moreover, three selected studies have proposed some VR systems that can be easily controlled with one hand (Fordell et al., 2011; Kim et al., 2011), this is a great advantage for USN patients since hemiparesis is extremely common. Given this disability, it is very important to analyze usability aspects of the setting as Kim et al. (2011), Mainetti et al. (2013), Navarro et al. (2013), and van Kessel et al. (2013) did for their tools.

A second critical challenge for the clinician is the technical usability of the VR system/software since the clinical staff often has no programming skills. For this reason, cooperation with software developers is necessary for the use and customization of the technology. By designing intuitive VR applications and providing adequate training, developers may also help medical personnel in using these tools independently. First of all, Mainetti et al. (2013) emphasized the necessity of close collaboration between technical and clinical staff to tailor virtual environments to the specific requirements of patients. Moreover, three selected studies specifically addressed these issues, emphasizing the need for an easy-to-use application (Fordell et al., 2011; Sugarman et al., 2011; Sedda et al., 2013). Sugarman et al. (2011) have commented on their special attention to the usability aspects of their system, specifying that "SeeMe does not require any equipment beyond a webcam camera and a standard computer with a good video card" (p. 1). Indeed, there is a growing diffusion of VR-based telerehabilitation systems for post-stroke patients (for a review, see Brochard et al., 2010), which has allowed new directions for the design of ecological scenarios supporting multimodal interaction (Perez-Marcos et al., 2012).

The third important challenge that may limit the use of VR in the assessment and rehabilitation of USN is the high costs often required for designing and testing a technological system. Our analysis showed that only two selected studies have tried to pay particular attention to the costs (Kim et al., 2011; Mainetti et al., 2013), while the others tried to use cutting-edge technology in order to maximize the performance of the system.

Specifically for the neuropsychological rehabilitation of USN, it is essential to take into account the specific needs of the different patients. For this reason, a more customizable neuropsychological rehabilitation would be essential. A platform that allows the clinician to customize the tasks might also make a difference.

Finally, all the articles analyzed suggest several methods for the assessment and rehabilitation of USN, but there are some "methodological weaknesses." Few studies compared VR methods with conventional ones (Kim et al., 2010, 2011; Mesa-Gresa et al., 2011; van Kessel et al., 2013; Aravind and Lamontagne, 2014; Aravind et al., 2015), only few studies compared the results with a control group (Kim et al., 2010; Peskine et al., 2011; Buxbaum et al., 2012; Navarro et al., 2013) and often the samples were too small to allow a generalization of the result (Peskine et al., 2011; Sugarman et al., 2011; Mainetti et al., 2013; Aravind and Lamontagne, 2014; Aravind et al., 2015), while controlled randomized trials testing the VR training in comparison with traditional protocol should be important. For further research, we also recommend adequate follow-up to maximize the benefits and monitor the persistence of the effect of neglect rehabilitation interventions. More, to enhance the potentiality of a multi-sensory and engaging VR stimulation, it is reasonable that USN patients should start a VR rehabilitation program in the acute stage.

However, the results obtained from the reviewed studies are promising and showed that VR systems stimulate interest and participation of patients (Kim et al., 2011). Indeed, VR simulations can be highly engaging by supporting a process known as "transformation of flow" (Riva et al., 2006), defined as an individual's ability to use and identify an optimal experience (i.e., flow) to promote new and unexpected psychological resources. This process may be particularly important since rehabilitation programs can be particularly demanding for patients. However, it is crucial to take into account potential transient side effects of immersive VR, such as cyber-sickness which occurs as a result of conflicts between visual, vestibular and proprioceptive signals. In addition to technological advancements, reducing the VR sessions (i.e., between 20 and 30 min) and giving precise explanations may alleviate any symptoms of discomfort.

Despite the great improvements in technology over the last 6 years, very few articles use new tools for assessment or rehabilitation in neuropsychology. The new technology systems for VR and the devices for "communication" with the virtual world could be very useful for neuropsychology; the possibility of acting in a virtual environment like in the real one is an important goal. Many efforts are aimed at improving the immersive virtual reality system, and there are two particularly important tools: VR wearable visors and the Cave Automatic Virtual Environment (CAVE). The VR head-mounted display is developed for virtual reality systems and video games. This tool uses custom tracking technology and creates a stereoscopic 3D view with excellent depth, scale and parallax by presenting unique and parallel images for each eye and using a 3-axis gyroscope, accelerometer and magnetometer to process data. The CAVE is a room with projection screens on the walls, floors and, in some cases, ceiling. The stereoscopic projectors are used for a 3D effect. These characteristics, together with the high-resolution of the graphics, allow an increase in the sense of presence. Users in the CAVE use head-trackers and hand-trackers in order to allow natural movements to interact with the virtual environment. CAVE is used mostly for design and fashion applications, but recently there have been some clinical applications, principally for the treatment of phobias and emotional disorders (Meyerbröker et al., 2010; Bouchard et al., 2013).

In terms of input devices, the classics are controllers for game consoles like Wii or Xbox. Wired gloves could be a way to improve the usability and comfort of the interaction and allow more fluid and natural movement in the environment. To remove the intermediation of tools, a solution could be using cameras to recognize models and identify motion, like Kinect or Vicon.

One input and output device is the Haptic device that allows people to feel the physical characteristics of the environment like gravity and viscosity.

The critical aspects of these devices are the high price and the complexity of both software and hardware components. To implement this device, support from technicians and developers is necessary in order to create the environments. Despite this limitation, this device has great potential to improve clinical practice. This new device allows for a completely different interaction with the virtual world and offers endless opportunities to analyze subject behavior in multiple ecological and controlled situations.

The aim of future studies could be to explore these possibilities in order to better understand the characteristics of each patient and his disorder and to create customized rehabilitation programs.

Additionally, the development of portable devices with good performance and reasonable prices may improve research concerning telemedicine, which would open the door to patients being treated at home without sacrificing medical supervision. Patients and doctors would be linked by a virtual platform that would allow monitoring of the patient's progress. The medical data could be mixed with the cognitive to make a complete picture of the healthy state of the patient. Medical data can be recorded by a wearable device capable of acquiring physiological signals.

Acknowledgments

This work was supported by the Italian funded project VRehab. Virtual Reality in the Assessment and TeleRehabilitation of Parkinson's Disease and "Post-Stroke Disabilities" - RF-2009-1472190.

References

Agrell, B. M., Dehlin, O. I., and Dahlgren, C. J. (1997). Neglect in elderly stroke patients: a comparison of five tests. *Psychiatry Clin. Neurosci.* 51, 295–300. doi: 10.1111/j.1440-1819.1997.tb03201.x

Albert, M. L. (1973). A simple test of visual neglect. *Neurology* 23, 658–664. doi: 10.1212/WNL.23.6.658

Appelros, P., Karlsson, G. M., Seiger, A., and Nydevik, I. (2002). Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. *J. Rehabil. Med.* 34, 215–220. doi: 10.1080/165019702760279206

Aravind, G., Darekar, A., Fung, J., and Lamontagne, A. (2015). Virtual reality-based navigation task to reveal obstacle avoidance performance in individuals with visuospatial neglect. *IEEE Trans. Neural Syst. Rehabil. Eng.* 23, 179–188. doi: 10.1109/TNSRE.2014.2369812

Aravind, G., and Lamontagne, A. (2014). Perceptual and locomotor factors affect obstacle avoidance in persons with visuospatial neglect. *J. Neuroeng. Rehabil.* 11:38. doi: 10.1186/1743-0003-11-38

Army Individual Test Battery. (1944). *Manual of Directions and Scoring.* Washington, DC: War Department, Adjutant General's Office.

Azouvi, P., Bartolomeo, P., Beis, J. M., Perennou, D., Pradat-Diehl, P., and Rousseaux, M. (2006). A battery of tests for the quantitative assessment of unilateral neglect. *Restor. Neurol. Neurosci.* 24, 273–285.

Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., and Tesio, L. (2003). Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego Scale. *Arch. Phys. Med. Rehabil.* 84, 51–57. doi: 10.1053/apmr.2003.50062

Bartolomeo, P., and Chokron, S. (2002). Orienting of attention in left unilateral neglect. *Neurosci. Biobehav. Rev.* 26, 217–234. doi: 10.1016/S0149-7634(01)00065-3

Bohil, C. J., Alicea, B., and Biocca, F. A. (2011). Virtual reality in neuroscience research and therapy. *Nat. Rev. Neurosci.* 12, 752–762. doi: 10.1038/nrn3122

Bonato, M. (2012). Neglect and extinction depend greatly on task demands: a review. *Front. Hum. Neurosci.* 6:195. doi: 10.3389/fnhum.2012.00195

Bonato, M., and Deouell, L. Y. (2013). Hemispatial neglect: computer-based testing allows more sensitive quantification of attentional disorders and recovery and might lead to better evaluation of rehabilitation. *Front. Hum. Neurosci.* 7:162. doi: 10.3389/fnhum.2013.00162

Bonato, M., Priftis, K., Marenzi, R., Umiltà, C., and Zorzi, M. (2012). Deficits of contralesional awareness: a case study on what paper-and-pencil tests neglect. *Neuropsychology* 26, 20. doi: 10.1037/a0025306

Bouchard, S., Bernier, F., Boivin, É., Dumoulin, S., Laforest, M., Guitard, T., et al. (2013). Empathy toward virtual humans depicting a known or unknown person expressing pain. *Cyberpsychol. Behav. Soc. Netw.* 16, 61–71. doi: 10.1089/cyber.2012.1571

Bowen, A., Hazelton, C., Pollock, A., and Lincoln, N. B. (2013). Cognitive rehabilitation for spatial neglect following stroke. *Cochrane Database Syst. Rev.* 7:CD0035860 doi: 10.1002/14651858.CD003586.pub3

Bowen, A., McKenna, K., and Tallis, R. C. (1999). Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. *Stroke* 30, 1196–1202. doi: 10.1161/01.STR.30.6.1196

Brochard, S., Robertson, J., Médée, B., and Rémy-Néris, O. (2010). What's new in new technologies for upper extremity rehabilitation? *Curr. Opin. Neurol.* 23, 683–687. doi: 10.1097/WCO.0b013e32833f61ce

Brooks, B. M., and Rose, F. D. (2003). The use of virtual reality in memory rehabilitation: Current findings and future directions. *NeuroRehabilitation* 18, 147–157.

Butter, C. M., Kirsch, N. L., and Reeves, G. (1990). The effect of lateralized dynamic stimuli on unilateral spatial neglect following right hemisphere lesions. *Restor. Neurol. Neurosci.* 2, 39–46.

Buxbaum, L. J., Dawson, A. M., and Linsley, D. (2012). Reliability and validity of the Virtual Reality Lateralized Attention Test in assessing hemispatial neglect in right-hemisphere stroke. *Neuropsychology* 26, 430. doi: 10.1037/a0028674

Buxbaum, L. J., Ferraro, M. K., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., et al. (2004). Hemispatial neglect: subtypes, neuroanatomy, and disability. *Neurology* 62, 749–756. doi: 10.1212/01.WNL.0000113730.73031.F4

Buxbaum, L. J., Palermo, M. A., Mastrogiovanni, D., Read, M. S., Rosenberg-Pitonyak, E., Rizzo, A. A., et al. (2008). Assessment of spatial attention and neglect with a virtual wheelchair navigation task. *J. Clin. Exp. Neuropsychol.* 30, 650–660. doi: 10.1080/13803390701625821

Cocchini, G., Beschin, N., and Jehkonen, M. (2001). The fluff test: a simple task to assess body representation neglect. *Neuropsychol. Rehabil.* 11, 17–31. doi: 10.1080/09602010042000132

Colarusso, R. P., and Hammill, D. D. (1972). *Motor-free Visual Perception Test.* Novato, CA: Academic Therapy Pub.

Corbetta, M., and Shulman, G. L. (2011). Spatial neglect and attention networks. *Annu. Rev. Neurosci.* 34, 569. doi: 10.1146/annurev-neuro-061010-113731

Corbetta, M., Kincade, M. J., Lewis, C., Snyder, A. Z., and Sapir, A. (2005). Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat. Neurosci.* 8, 1603–1610. doi: 10.1038/nn1574

Dalmaijer, E. S., Van der Stigchel, S., Nijboer, T. C., Cornelissen, T. H., and Husain, M. (2014). CancellationTools: All-in-one software for administration and analysis of cancellation tasks. *Behav. Res. Methods*. doi: 10.3758/s13428-014-0522-7. [Epub ahead of print].

DE RENZI, E., and VIGNOLO, L. A. (1962). The token test: a sensitive test to detect receptive disturbances in aphasics. *Brain* 85, 665. doi: 10.1093/brain/85.4.665

Deouell, L. Y., Sacher, Y., and Soroker, N. (2005). Assessment of spatial attention after brain damage with a dynamic reaction time test. *J. Int. Neuropsychol. Soc.* 11, 697–707. doi: 10.1017/s1355617705050824

Di Carlo, A. (2009). Human and economic burden of stroke. *Age Ageing* 38, 4–5. doi: 10.1093/ageing/afn282

Diller, L., and Weinberg, J. (1976). Hemi-inattention in rehabilitation: the evolution of a rational remediation program. *Adv. Neurol.* 18, 63–82.

Dvorkin, A. Y., Rymer, W. Z., Settle, K., and Patton, J. L. (2007). "Perceptual assessment of spatial neglect within a virtual environment," in *Paper Presented at the Virtual Rehabilitation* (Venice).

Eslinger, P. J., Flaherty-Craig, C. V., and Benton, A. L. (2004). Developmental outcomes after early prefrontal cortex damage. *Brain Cogn.* 55, 84–103. doi: 10.1016/S0278-2626(03)00281-1

Eslinger, P. J., Grattan, L. M., Damasio, H., and Damasio, A. R. (1992). Developmental consequences of childhood frontal lobe damage. *Arch. Neurol.* 49, 764–769. doi: 10.1001/archneur.1992.00530310112021

Folstein, M. F., Robins, L. N., and Helzer, J. E. (1983). The Mini-mental state examination. *Arch. Gen. Psychiatry* 40, 812. doi: 10.1001/archpsyc.1983.01790060110016

Fordell, H., Bodin, K., Bucht, G., and Malm, J. (2011). A virtual reality test battery for assessment and screening of spatial neglect. *Acta Neurol. Scand.* 123, 167–174. doi: 10.1111/j.1600-0404.2010.01390.x

Gauthier, L., Dehaut, F., and Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *Int. J. Clin. Neuropsychol.* 11, 49–54.

Geeraerts, S., Lafosse, C., Vandenbussche, E., and Verfaillie, K. (2005). A psychophysical study of visual extinction: ipsilesional distractor interference with contralesional orientation thresholds in visual hemineglect patients. *Neuropsychologia* 43, 530–541. doi: 10.1016/j.neuropsychologia.2004.07.012

Gontkovsky, S. T., McDonald, N. B., Clark, P. G., and Ruwe, W. D. (2002). Current directions in computer-assisted cognitive rehabilitation. *NeuroRehabilitation* 17, 195–199.

Hackett, M. L., Yapa, C., Parag, V., and Anderson, C. S. (2005). Frequency of depression after stroke a systematic review of observational studies. *Stroke* 36, 1330–1340. doi: 10.1161/01.STR.0000165928.19135.35

Halligan, P. W., Fink, G. R., Marshall, J. C., and Vallar, G. (2003). Spatial cognition: evidence from visual neglect. *Trends Cogn. Sci.* 7, 125–133. doi: 10.1016/S1364-6613(03)00032-9

Halligan, P. W., Marshall, J. C., and Wade, D. T. (1989). Visuospatial neglect: underlying factors and test sensitivity. *Lancet* 334, 908–911. doi: 10.1016/S0140-6736(89)91561-4

Heilman, K. M., Watson, R. T., and Valenstein, E. (1985). *Neglect and Related Disorders.* New York, NY: Oxford University Press.

Hendricks, H. T., van Limbeek, J., Geurts, A. C., and Zwarts, M. J. (2002). Motor recovery after stroke: a systematic review of the literature. *Arch. Phys. Med. Rehabil.* 83, 1629–1637. doi: 10.1053/apmr.2002.35473

Jacquin-Courtois, S., O'Shea, J., Luauté, J., Pisella, L., Revol, P., Mizuno, K., et al. (2013). Rehabilitation of spatial neglect by prism adaptation: a peculiar expansion of sensorimotor after-effects to spatial cognition. *Neurosci. Biobehav. Rev.* 37, 594–609. doi: 10.1016/j.neubiorev.2013.02.007

Jehkonen, M., Laihosalo, M., and Kettunen, J. (2006). Impact of neglect on functional outcome after stroke-a review of methodological issues and recent research findings. *Restor. Neurol. Neurosci.* 24, 209–215.

Jung, H. Y., Park, B. K., Shin, H. S., Kang, Y. K., Pyun, S. B., Paik, N. J., et al. (2007). Development of the Korean version of Modified Barthel Index (K-MBI): multi-center study for subjects with stroke. *J. Korean Acad. Rehabil. Med.* 31, 283–297.

Kerkhoff, G., and Schenk, T. (2012). Rehabilitation of neglect: an update. *Neuropsychologia* 50, 1072–1079. doi: 10.1016/j.neuropsychologia.2012.01.024

Kim, D. Y., Ku, J., Chang, W. H., Park, T. H., Lim, J. Y., Han, K., et al. (2010). Assessment of post-stroke extrapersonal neglect using a three-dimensional immersive virtual street crossing program. *Acta Neurol. Scand.* 121, 171–177. doi: 10.1111/j.1600-0404.2009.01194.x

Kim, Y. M., Chun, M. H., Yun, G. J., Song, Y. J., and Young, H. E. (2011). The effect of virtual reality training on unilateral spatial neglect in stroke patients. *Ann. Rehabil. Med.* 35, 309–315. doi: 10.5535/arm.2011.35.3.309

Làdavas, E., Shallice, T., and Zanella, M. T. (1997). Preserved semantic access in neglect dyslexia. *Neuropsychologia* 35, 257–270. doi: 10.1016/S0028-3932(96)00066-8

Langhorne, P., Coupar, F., and Pollock, A. (2009). Motor recovery after stroke: a systematic review. *Lancet Neurol.* 8, 741–754. doi: 10.1016/S1474-4422(09)70150-4

Leigh, S., Danckert, J., and Eliasmith, C. (2015). Modelling the differential effects of prisms on perception and action in neglect. *Exp. Brain Res.* 233, 751–766. doi: 10.1007/s00221-014-4150-3

Levick, W. R. (2010). Observer rating of memory in children: a review. *Brain Impair.* 11, 144–151. doi: 10.1375/brim.11.2.144

Lindell, A. B., Jalas, M. J., Tenovuo, O., Brunila, T., Voeten, M. J., and Hämäläinen, H. (2007). Clinical assessment of hemispatial neglect: evaluation of different measures and dimensions. *Clin. Neuropsychol.* 21, 479–497. doi: 10.1080/13854040600630061

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T. B., Flegal, K., et al. (2009). Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 119, 21–181. doi: 10.1161/CIRCULATIONAHA.108.191261

Mainetti, R., Sedda, A., Ronchetti, M., Bottini, G., and Borghese, N. A. (2013). Duckneglect: video-games based neglect rehabilitation. *Technol. Health Care* 21, 97–111. doi: 10.3233/THC-120712

Mattingley, J. B., Bradshaw, J. L., and Bradshaw, J. A. (1994). Horizontal visual motion modulates focal attention in left unilateral spatial neglect. *J. Neurol. Neurosurg. Psychiatry* 57, 1228–1235. doi: 10.1136/jnnp.57.10.1228

Mesa-Gresa, P., Lozano, J. A., Llórens, R., Alcañiz, M., Navarro, M. D., and Noé, E. (2011). "Clinical validation of a virtual environment test for safe street crossing in the assessment of acquired brain injury patients with and without neglect," in *Paper Presented at the Proceedings of the 13th IFIP TC 13 International Conference on Human-computer Interaction - Volume Part II* (Lisbon).

Meyerbröker, K., Morina, N., Kerkhof, G., and Emmelkamp, P. M. (2010). Virtual reality exposure treatment of agoraphobia: a comparison of computer automatic virtual environment and head-mounted display. *Stud. Health Technol. Inform.* 167, 51–56. doi: 10.3233/978-1-60750-766-6-51

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6:e1000097. doi: 10.1371/journal.pmed.1000097

Mutai, H., Furukawa, T., Araki, K., Misawa, K., and Hanihara, T. (2012). Factors associated with functional recovery and home discharge in stroke patients admitted to a convalescent rehabilitation ward. *Geriatr. Gerontol. Int.* 12, 215–222. doi: 10.1111/j.1447-0594.2011.00747.x

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Navarro, M. D., Lloréns, R., Noé, E., Ferri, J., and Alcañiz, M. (2013). Validation of a low-cost virtual reality system for training street-crossing. A comparative study in healthy, neglected and non-neglected stroke individuals. *Neuropsychol. Rehabil.* 23, 597–618. doi: 10.1080/09602011.2013.806269

Newport, R., and Schenk, T. (2012). Prisms and neglect: what have we learned? *Neuropsychologia* 50, 1080–1091. doi: 10.1016/j.neuropsychologia.2012.01.023

Nijboer, T. C., Kollen, B. J., and Kwakkel, G. (2013a). Time course of visuospatial neglect early after stroke: a longitudinal cohort study. *Cortex* 49, 2021–2027. doi: 10.1016/j.cortex.2012.11.006

Nijboer, T. C. W., Kollen, B. J., and Kwakkel, G. (2014a). The impact of recovery of visuo-spatial neglect on motor recovery of the upper paretic limb after stroke. *PLoS ONE* 9:e100584. doi: 10.1371/journal.pone.0100584

Nijboer, T. C. W., Ten Brink, A. F., Kouwenhoven, M., and Visser-Meily, J. M. A. (2014b). Functional assessment of region-specific neglect: are there differential behavioural consequences of peripersonal versus extrapersonal neglect? *Behav. Neurol.* 2014:526407. doi: 10.1155/2014/526407

Nijboer, T. C., van de Port, I., Schepers, V., Post, M., and Visser-Meily, A. (2013b). Predicting functional outcome after stroke: the influence of neglect on basic activities in daily living. *Front. Hum. Neurosci.* 7:182. doi: 10.3389/fnhum.2013.00182

Paci, M., Matulli, G., Baccini, M., Rinaldi, L. A., and Baldassi, S. (2010). Reported quality of randomized controlled trials in neglect rehabilitation. *Neurol. Sci.* 31, 159–163. doi: 10.1007/s10072-009-0198-4

Peña-Casanova, J., Gramunt Fombuena, N., and Gich Fullà, J. (2006). *Neurophychological Tests*. Barcelona: Elsevier.

Pendlebury, S. T., Giles, M. F., and Rothwell, P. M. (2009). *Transient Ischemic Attack and Stroke: Diagnosis, Investigation and Management.* Cambridge: Cambridge University Press.

Perez-Garcia, M., Godoy-Garcia, J. F., Vera-Guerrero, N., Laserna-Triguero, J. A., and Ouente, A. E. (1998). Neuropsychological evaluation of everyday memory. *Neuropsychol. Rev.* 8, 203–227. doi: 10.1023/A:1021622319851

Perez-Marcos, D., Solazzi, M., Steptoe, W., Oyekoya, O., Frisoli, A., Weyrich, T., et al. (2012). A fully-immersive set-up for remote interaction and neurorehabilitation based on virtual body ownership. *Front. Neurol.* 3:110. doi: 10.3389/fneur.2012.00110

Peskine, A., Rosso, C., Box, N., Galland, A., Caron, E., Rautureau, G., et al. (2011). Virtual reality assessment for visuospatial neglect: importance of a dynamic task. *J. Neurol. Neurosurg. Psychiatr.* 82, 1407–1409. doi: 10.1136/jnnp.2010.217513

Pflugshaupt, T., Bopp, S. A., Heinemann, D., Mosimann, U. P., von Wartburg, R., Nyffeler, T., et al. (2004). Residual oculomotor and exploratory deficits in patients with recovered hemineglect. *Neuropsychologia* 42, 1203–1211. doi: 10.1016/j.neuropsychologia.2004.02.002

Pierce, S. R., and Buxbaum, L. J. (2002). Treatments of unilateral neglect: a review. *Arch. Phys. Med. Rehabil.* 83, 256–268. doi: 10.1053/apmr.2002.27333

Pizzamiglio, L. (1990). *La Rieducazione Dell'Eminattenzione Spaziale.* Milano: Masson Ed.

Pohjasvaara, T., Leskelä, M., Vataja, R., Kalska, H., Ylikoski, R., Hietanen, M., et al. (2002). Post−stroke depression, executive dysfunction and functional outcome. *Eur. J. Neurol.* 9, 269–275. doi: 10.1046/j.1468-1331.2002.00396.x

Rabuffetti, M., Farina, E., Alberoni, M., Pellegatta, D., Appollonio, I., Affanni, P., et al. (2012). Spatio-temporal features of visual exploration in unilaterally brain-damaged subjects with or without neglect: results from a touchscreen test. *PLoS ONE* 7:e31511. doi: 10.1371/annotation/bf311a56-bc48-44b6-9b0f-7ccc97fc290f

Rengachary, J., d'Avossa, G., Sapir, A., Shulman, G. L., and Corbetta, M. (2009). Is the posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke? *Arch. Phys. Med. Rehabil.* 90, 2081–2088. doi: 10.1016/j.apmr.2009.07.014

Riva, G. (2009). Virtual reality: an experiential tool for clinical psychology. *Br. J. Guid. Couns.* 37, 337–345. doi: 10.1080/03069880902957056

Riva, G., Castelnuovo, G., and Mantovani, F. (2006). Transformation of flow in rehabilitation: the role of advanced communication technologies. *Behav. Res. Methods* 38, 237–244. doi: 10.3758/BF03192775

Riva, G., Mantovani, F., and Gaggioli, A. (2004). Presence and rehabilitation: toward second-generation virtual reality applications in neuropsychology. *J. Neuroeng. Rehabil.* 1, 9. doi: 10.1186/1743-0003-1-9

Rizzo, A. A., Buckwalter, J. G., and van der Zaag, C. (2002). "Applications for neuropsychological assessment and rehabilitation," in *Handbook of Virtual Environments,* ed K. Stanney (New York, NY: L. A. Earlbaum), 1027–1064.

Robertson, I. H., and Halligan, P. W. (1999). *Spatial Neglect: A Clinical Handbook for Diagnosis and Treatment*. Hove: Psychology Press.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., et al. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature* 395, 166–169. doi: 10.1038/25988

Schenkenberg, T., Bradford, D. C., and Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 30, 509–509. doi: 10.1212/WNL.30.5.509

Schultheis, M. T., and Rizzo, A. A. (2001). The application of virtual reality technology in rehabilitation. *Rehabil. Psychol.* 46, 296. doi: 10.1037/0090-5550.46.3.296

Sedda, A., Borghese, N. A., Ronchetti, M., Mainetti, R., Pasotti, F., Beretta, G., et al. (2013). Using virtual reality to rehabilitate neglect. *Behav. Neurol.* 26, 183–185. doi: 10.1155/2013/810279

Smania, N., Martini, M., Gambina, G., Tomelleri, G., Palamara, A., Natale, E., et al. (1998). The spatial distribution of visual attention in hemineglect and extinction patients. *Brain* 121, 1759–1770. doi: 10.1093/brain/121.9.1759

Smit, M., Van der Stigchel, S., Visser-Meily, J. M., Kouwenhoven, M., Eijsackers, A. L., and Nijboer, T. C. (2013). The feasibility of computer-based prism adaptation to ameliorate neglect in sub-acute stroke patients admitted to a rehabilitation center. *Front. Hum. Neurosci.* 7:353. doi: 10.3389/fnhum.2013.00353

Spinnler, H., and Tognoni, G. (1987). *Standardizzazione e Taratura Italiana di Test Neuropsicologici*. Milano: Masson Italia Periodici.

Sudlow, C. L. M., and Warlow, C. P. (1997). Comparable studies of the incidence of stroke and its pathological types - Results from am international collaboration. *Stroke* 28, 491–499. doi: 10.1161/01.STR.28.3.491

Sugarman, H., Weisel-Eichler, A., Burstin, A., and Brown, R. (2011). "Use of novel virtual reality system for the assessment and treatment of unilateral spatial neglect: A feasibility study," in *Paper Presented 2011 International Conference on the Virtual Rehabilitation (ICVR)* (Zurich). doi: 10.1109/ICVR.2011.5971859

Sundar, U., and Adwani, S. (2010). Post-stroke cognitive impairment at 3 months. *Ann. Indian Acad. Neurol.* 13, 42. doi: 10.4103/0972-2327.61276

Tanaka, T., Ifukube, T., Sugihara, S., and Izumi, T. (2010). A case study of new assessment and training of unilateral spatial neglect in stroke patients: effect of visual image transformation and visual stimulation by using a head mounted display system (HMD). *J. Neuroeng. Rehabil.* 7:20. doi: 10.1186/1743-0003-7-20

Tant, M. L. M., Kuks, J. M. B., Kooijman, A. C., Cornelissen, F. W., and Brouwer, W. H. (2002). Grey scales uncover similar attentional effects in homonymous hemianopia and visual neglect. *Neuropsychologia* 40, 1474–1481. doi: 10.1016/S0028-3932(01)00197-X

Tham, K. (1996). The baking tray task: a test of spatial neglect. *Neuropsychol. Rehabil.* 6, 19–26. doi: 10.1080/713755496

Tham, K., and Tegnér, R. (1996). The baking tray task: a test of spatial neglect. *Neuropsychol. Rehabil.* 6, 19–25. doi: 10.1080/713755496

Towle, D., and Lincoln, N. B. (1991). Development of a questionnaire for detecting everyday problems in stroke patients with unilateral neglect. *Clin. Rehabil.* 5, 135–140. doi: 10.1177/026921559100500208

Tsirlin, I., Dupierrix, E., Chokron, S., Coquillart, S., and Ohlmann, T. (2009). Uses of virtual reality for diagnosis, rehabilitation and study of unilateral spatial neglect: review and analysis. *Cyberpsychol. Behav.* 12, 175–181. doi: 10.1089/cpb.2008.0208

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., et al. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behav. Res. Methods* 47, 27–44. doi: 10.3758/s13428-014-0448-0

Vallar, G., and Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia* 24, 609–622. doi: 10.1016/0028-3932(86)90001-1

van Kessel, M. E., Geurts, A. C., Brouwer, W. H., and Fasotti, L. (2013). Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task. *Front. Hum. Neurosci.* 7:358. doi: 10.3389/fnhum.2013.00358

Vriezen, E. R., Pigott, S. D., and Pelletier, P. M. (2001). Developmental implications of early frontal-lobe damage: a case study. *Brain Cogn.* 47, 222–225.

Wilson, B., Cockburn, J., and Halligan, P. (1987). Development of a behavioral test of visuospatial neglect. *Arch. Phys. Med. Rehabil.* 68, 98–102.

Witmer, B., and Singer, M. (1998). Measuring presence in virtual environments: a presence questionnaire. *Presence* 7, 225–240. doi: 10.1162/105474698565686

Wolfe, C. D. A. (2000). The impact of stroke. *Br. Med. Bull.* 56, 275–286. doi: 10.1258/0007142001903120

Yong Joo, L., Soon Yin, T., Xu, D., Thia, E., Pei Fen, C., Kuah, C. W., et al. (2010). A feasibility study using interactive commercial off-the-shelf computer gaming in upper limb rehabilitation in patients after stroke. *J. Rehabil. Med.* 42, 437–441. doi: 10.2340/16501977-0528

Zhang, Y., Chapman, A. M., Plested, M., Jackson, D., and Purroy, F. (2012). The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke Res. Treat.* 2012:436125. doi: 10.1155/2012/436125

Zoccolotti, P., Antonucci, G., and Judica, A. (1992). Psychometric characteristics of two semi-structured scales for the functional evaluation of hemi-inattention in extrapersonal and personal space. *Neuropsychol. Rehabil.* 2, 179–191. doi: 10.1080/09602019208401407

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 12 August 2015
doi: 10.3389/fnbeh.2015.00211

Improving memory following prefrontal cortex damage with the PQRST method

Elisa Ciaramelli[1,2], Francesco Neri[2], Luca Marini[2] and Davide Braghittoni[2]*

[1] Dipartimento di Psicologia, Università di Bologna, Bologna, Italy, [2] Centro di Studi e Ricerche in Neuroscienze Cognitive, Cesena, Italy

We tested (1) whether the PQRST method, involving Preview (P), Question (Q), Read (R), State (S), and Test (T) phases, is effective in enhancing long-term memory in patients with mild memory problems due to prefrontal cortex lesions, and (2) whether patients also benefit from a more self-initiated version of the PQRST. Seven patients with prefrontal lesions encoded new texts under three different conditions: the Standard condition, requiring to read texts repeatedly, the PQRST-Other condition, in which the experimenter formulated questions about the text (Q phase), and the PQRST-Self condition, in which patients formulated the relevant questions on their own. Compared to the Standard condition, both the PQRST-Other and the PQRST-Self condition resulted in higher immediate and delayed recall rates, as well as a higher ability to answer questions about the texts. Importantly, the two PQRST conditions did not differ in efficacy. These results confirm that the PQRST method is effective in improving learning of new material in brain-injured populations with mild memory problems. Moreover, they indicate that the PQRST proves effective even under conditions with higher demands on patients' autonomy and self-initiation, which encourages its application to real-life situations.

Keywords: long-term memory, episodic memory, cognitive rehabilitation, prefrontal cortex, amnesia

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Radek Ptak, Geneva University Hospitals, Switzerland
Jee Hyun Kim, University of Melbourne, Australia

****Correspondence:***
Elisa Ciaramelli, Dipartimento di Psicologia, Università di Bologna, Viale Berti-Pichat 5, 40126 Bologna, Italy
elisa.ciaramelli@unibo.it

Received: *30 April 2015*
Accepted: *28 July 2015*
Published: *12 August 2015*

Citation:
Ciaramelli E, Neri F, Marini L and Braghittoni D (2015) Improving memory following prefrontal cortex damage with the PQRST method. Front. Behav. Neurosci. 9:211. doi: 10.3389/fnbeh.2015.00211

Introduction

Long-term memory disorders are among the most challenging cognitive impairments following acquired brain damage, and may have a profound impact on patients' daily living, ranging from minimal forgetfulness to a pervasive inability to learn new information and cope with life demands. For this reason, there is great interest in developing methods aimed at restoring or compensating memory impairment.

Memory is a multicomponential process. Consequently, memory deficits are multifaceted, and call for different treatment options. Lesions to the medial temporal lobe may result in an inability to explicitly encode and retrieve new information, while implicit memory is spared (Kopelman, 2002; Wilson, 2009). Damage to the prefrontal cortex more commonly hampers "working-with-memory" processes supporting encoding and retrieval operations (Moscovitch, 1992; Shimamura, 1995). Prefrontal cortex may assist encoding operations by favoring selection of goal-relevant incoming information (Otten et al., 2001; Badre and Wagner, 2007; Blumenfeld and Ranganath, 2007) and its meaningful organization in working memory (Fletcher and Henson, 2001; Blumenfeld and Ranganath, 2007). At retrieval, prefrontal cortex may support selection of relevant memories according to retrieval goals

(Kuhl et al., 2007; Barredo et al., 2015) and monitoring processes assessing the veridicality of the retrieval output (Gilboa and Moscovitch, 2002; Ciaramelli and Spaniol, 2009).

While treatment options for severe amnesia include techniques based on spared implicit memory processes and memory aids (Baddeley and Wilson, 1994; Wilson, 2009; Ptak et al., 2010), patients with less severe deficits and partial sparing of explicit memory may benefit from "internal" mnemonics directed at optimizing encoding and retrieval operations (Van der Linden and Van der Kaa, 1989; Ptak et al., 2010). These include the generation of images connected to the material to be learned (e.g., Jones, 1974; Kaschel et al., 2002), verbal strategies (Harris, 1992), and optimal structuring of information (Doornheim and De Haan, 1998). The PQRST method is one such strategy (Moffat, 1992).

PQRST is the acronym of *Preview* (establish the general theme of the text), *Question* (formulate main questions about the text), *Read* (read carefully, thinking at the questions), *State* (summarize the main information), and *Test* (test your knowledge) (Moffat, 1992). This method drives individuals through an ordinated series of steps favoring deep analysis and organization of texts to be learned, which improves later retention (Wilson, 2009).

Wilson (1987, 2009) has tested the efficacy of PQRST empirically in several cases of memory-impaired patients. First, she described a few cases of patients with severe amnesia due to various etiologies who studied newspaper articles either under PQRST instructions or repeated practice instructions (i.e., they were read the passages several times). Compared to repeated practice, PQRST generally led to an improvement in answering questions about the text. Since questions were part of the PQRST learning procedure, however, the observed improvement may be due to "encoding specificity," the reinstatement of the original learning situation at recall (Tulving and Thomson, 1973). Patients, indeed, did not improve in free recall, suggesting that PQRST brings little benefit to patients with severe amnesia (Wilson, 1987). Different seems the case of patients with less severe memory deficits. In a group of patients with mild memory deficits due to traumatic brain injury (TBI), the PQRST method led to an improvement not only in answering questions about the texts, but also in (delayed) recall (Wilson, 1987). In this case, the improvement could not be explained by encoding specificity alone. Rather, the PQRST seems to optimize encoding operations, though it is not completely clear through which mechanisms. One candidate mechanism is deep encoding. According to Craik and Lockhart (1972), material processed at a deep (e.g., semantic) level is retained better than information processed at a shallow (e.g., phonological) level, and PQRST (compared to repeated practice) demands a deeper semantic analysis of the text in order to answer the relevant questions. More recently, Franzen et al. (1996) have applied the PQRST to two young TBI patients. Both patients improved following the PQRST compared to a control "metacognitive" treatment, but returned to baseline levels soon (Franzen et al., 1996). As well, Bussman-Mork et al. (2000) noted that PQRST led to better retention of new material compared to no-treatment, but that it was lacking in generalization (Wilson, 2009). In sum, there is some evidence that the PQRST method is effective in improving long-term memory in patients with mild memory deficits, but there are not many studies evaluating its efficacy. Moreover, extant studies raise concerns about the generalization of training effects.

The first aim of this study is to test the efficacy of the PQRST method in a group of patients with mild memory problems due prefrontal cortex lesions. Given that prefrontal cortex supports strategic encoding and retrieval processes (Moscovitch, 1992), and that patients with prefrontal lesions may fail to adopt strategies spontaneously (Stuss et al., 1994; Gershberg and Shimamura, 1995; Alexander et al., 2009), we predict that this patient population should benefit enormously from strategic encoding conditions such as those promoted by the PQRST method. One second aim of the study pertains to the "Question phase" of the PQRST, which constitutes the "skeleton" around which the PQRST procedure unfolds. In principle, questions about the main aspects of the text may be formulated by the experimenter or the patients themselves. Previous studies have mainly adopted questions formulated by the experimenter, and no study so far has investigated whether the two strategies are equally effective. Of course, severely compromised patients may not be able to formulate questions on their own. However, if they are, one may predict an even larger effect of PQRST using self-generated questions, compared to other-generated question. Self-generated questions would reflect those aspects of the text that captured patients' attention, and would therefore be ideally suited to motivate patients to scrutinize the texts further. Recall, indeed, tends to be better for information that is more personally salient (e.g., Westmacott and Moscovitch, 2003). Understanding the effectiveness of self-generated questions would be important with respect to generalization. Generalization, that is, the spontaneous transfer of a trained technique to new material and real-life situations, is the ultimate goal of cognitive rehabilitation. One prerequisite for the spontaneous use of the PQRST in real life is the ability, on the patients' part, to formulate questions on their own. Demonstrating that the PQRST method also works with self-generated questions, therefore, would be one first step toward promoting its use in real life.

To these aims, a group of patients with prefrontal lesions memorized texts in three different encoding conditions: a Standard condition, requiring to read the text repeatedly (see below), and two different PQRST conditions; in one, the questions were created by the experimenter (PQRST-Other condition), whereas in the other questions were created by the patients themselves (PQRST-Self condition). To foreshadow the results, we found that, compared to the Standard condition, both the PQRST-Other condition and the PQRST-Self condition resulted in better memory for the texts. Importantly, the PQRST-Self condition proved as effective as the PQRST-Other condition.

Materials and Methods

Participants

Participants were seven patients (one female) with lesions to the prefrontal cortex due to anterior communicating artery (AcoA) aneurysm or TBI (see **Table 1** for demographic and clinical data). Patients had a mean age of 45 years (range 32–60),

TABLE 1 | Patients' demographic and clinical data.

Patients:	C.C.	G.V.	A.B.	S.S.	C.2.	E.L.	V.2.	Mean
Age	41	52	60	51	32	31	48	45.0
Education	13	8	13	8	13	13	13	11.6
Gender	M	M	M	M	M	M	F	
Time since lesion (years)	1	7	6	1	13	4	20	7.4
Etiology	AcoA aneurysm	AcoA aneurysm	AcoA aneurysm	AcoA aneurysm	AcoA aneurysm	TBI	TBI	
Brain Damage	Bilateral vmPFC	Bilateral vmPFC, more pronounced on the right	Bilateral vmPFC	Bilateral vmPFC	Bilateral vmPFC	Bilateral frontal and temporal poles	Left prefrontal cortex	
MMSE	28	24	24	28	30	25	28	26.7
Attentional matrices	43 (2)	51 (4)	47 (3)	53 (4)	38 (2)	48 (3)	44 (3)	46.3 (3)
Stroop test-Errors (raw score)	1	0	0	0	0	0	0	0.1
WCST-Perseverative errors (%)(in percentile)	36 (1)	47 (1)	20 (30)	57 (1)	1 (50)	29 (1)	4 (50)	27.7(19.1)
Phonemic fluency	18 (1)	22 (1)	38 (4)	29 (3)	27 (3)	19 (1)	29 (3)	26.0 (2.2)
Semantic fluency	30 (2)	40.5 (4)	52 (4)	48 (4)	58 (4)	29 (1)	63 (4)	45.7(3.2)
Corsi test	3.5 (1)	4.5 (3)	3.75 (1)	6 (4)	3.5 (1)	4.5 (3)	5.75 (4)	4.5 (2.4)
Digit span	4.5 (2)	5 (3)	4.75 (4)	6 (4)	5.25 (4)	5.5 (4)	4.5 (2)	5.0 (3.2)
Word-list learning*-Immediate	0	0	1	3	3	0	0	1
-Delayed*	2	0	0	0	0	0	0	0.28
Prose passage recall task*	2	0	1	1	0	1	2	1
WMS	101	79	92	84	77	83	96	87.4

*F, female; M, male; ACoA, anterior communicating artery; TBI, traumatic brain injury; WMS, Weschler Memory Scale. Unless noted, we report corrected scores, with the corresponding equivalent score (ES) in parentheses. *in these cases, we report ES only, because different versions of the test were used across patients, and therefore corrected scores are not comparable.*

and a mean education of 11.57 years (range 8–13). Time since injury was, on average, 7.4 years (range 1–20). Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience of the University of Bologna, in the context of a routine neuropsychological assessment, which highlighted, in all cases, long-term memory deficits. All patients complained about memory deficits in real life, and participated voluntarily to the study. Included patients were not receiving psychoactive drugs, and had no other diagnosis likely to affect cognition or interfere with the participation in the study (e.g., significant psychiatric disease, alcohol abuse, history of cerebrovascular disease) as determined by history. Participants gave written informed consent to participate in the study according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the Ethical Committee of the Department of Psychology, University of Bologna.

Neuropsychological Profile

Patients' general cognitive functioning was generally preserved, as indicated by the scores they obtained in the Mini Mental State Examination, which were within the normal range in all cases ($M = 26.7$). Patients performed normally also in several tests assessing attentional and executive functions, such as selective attention (assessed with the Attentional Matrices test; Equivalent score (ES) = 3. Note that the ES ranges from 0 = impaired performance, and 1 = borderline performance, to 2–4 indicating normal performance; Spinnler and Tognoni, 1987), inhibition of automatic responses (assessed with the Stroop Color–Word test; mean number of errors = 0.14, cut off >7.5), semantic fluency (ES = 3.2; Spinnler and Tognoni, 1987) and phonemic fluency (ES = 2.2; Spinnler and Tognoni, 1987). Patients showed a weak performance in the Wisconsin Card Sorting Test, which was characterized by several perseverative errors (mean percentile score = 19.1). All patients, however, exhibited long-term memory deficits (Spinnler and Tognoni, 1987). On the Wechsler Memory Scale (Wechsler, 1945; Barletta-Rodolfi et al., 2011), patients' mean general memory index was borderline ($M = 87.4$). Performance in immediate recall of word lists (assessed either with the Buschke–Fuld Test or the Rey 15 words test; Barletta-Rodolfi et al., 2011) and of a prose-passage recall task was weak (ES = 1 in both cases), and delayed recall of word lists was highly pathological (ES = 0.28; Spinnler and Tognoni, 1987). In contrast, scores in verbal short-term memory (ES = 3.2) and spatial short-term memory (ES = 2.4; assessed with Digit Span and Corsi test, respectively) were normal (Spinnler and Tognoni, 1987).

Materials

Twenty-four prose passages were selected and adapted from various online media (e.g., online newspapers) as well as the reading comprehension section of a high school book. Each passage was between 145 and 190 words in length ($M = 172$, SD = 13), covered a single topic, and was divided into 28–30 idea units for scoring purposes. For each passage, four questions were developed, covering the main aspects of the story (other-generated questions; see below). The 24 prose passages were randomly divided into three sets of eight passages, matched for number of words [$F(2,21) = 0.47$; $p = 0.62$] and units [$F(2,21) = 0.24$; $p = 0.78$]. The assignment of the three sets to the different experimental conditions (Standard, PQRST-Other, PQRST-Self) was counterbalanced across participants.

Procedures

The 24 prose passages were administered in 24 different experimental sessions. The alternance of experimental conditions across sessions was counterbalanced across participants (e.g., day 1: PQRST-Self; day 2: Standard; day 3: PQRST-Other: day 4: PQRST-Self, and so on), and the order of administration of each prose passage within each set was determined randomly for each participant. Depending on the experimental condition, participants received different encoding instructions.

PQRST-Other Condition and PQRST-Self Condition

In the Preview (P) phase, the experimenter read the passage aloud, to make the participants get a general idea of the material. The Question (Q) phase was different in the PQRST-Other and PQRST-Self conditions: in the PQRST-Other condition, the experimenter read the four (other-generated) questions about the text (e.g., How did the fireman solve the problem of the five people?). In the PQRST-Self condition, the patient formulated four questions regarding the text (self-generated questions). The experimenter stressed the need to formulate four questions that covered the whole story. In both PQRST conditions, the four questions were written on a card that was placed on the desk, in front of the participant, and remained there throughout the Read phase (R), in which participants read the material carefully to look for the answers to the questions. In the following State (S) phase, patients stated the answers, and, if necessary, read the text again. The whole "study session" lasted 10 min on average. Immediately afterward, the Test (T) phase began, in which the experimenter tested memory for the text by (1) asking the same questions that had been embedded in the study phase (i.e., the other-generated questions in the PQRST-Other condition, and the self-generated questions in the PQRST-Self condition), (2) asking for free recall of the passage, and (3) asking for delayed free recall of the passage, after 10 min of non-interfering activities (e.g., videogames). In the PQRST-Self condition, after delayed recall of the self-generated questions, patients were also asked the other-generated questions, i.e., those commonly used in the PQRST-Other condition. This was done to verify whether the improvement in answering questions about a text was limited to those questions that were part of the procedure, or generalized to untrained questions.

Standard Condition

The standard condition was designed to (1) be representative of patients' usual encoding strategies and (2) last as long as the PQRST-based conditions. A preliminary, informal interview with each patient and a relative revealed that patients' most common strategy to learn new material was to re-read texts over and over again, and in some cases highlight the relevant parts. In a second session, the experimenter asked patients to memorize a text, which confirmed that this was indeed the most frequent learning strategy they adopted. The Standard enconding condition was designed to mimic patients' spontaneous strategies. First, similar to the two PQRST conditions, the experimenter read the passage aloud (Preview phase). Patients were then left free to read the text over and over again for 10 min, during which they could take notes and underline the most important parts (Study phase). Importantly, also in the Standard condition patients had the four questions about the passage introduced early on, which remained in front of them for the entire duration of the Study phase (see also Wilson, 1987). Patients were told that those questions highlighted the principal parts of the passage. This was done to verify if the mere availability of the four relevant questions accounted for performance improvements in the two PQRST conditions. After the study phase, patients were tested for retention in the same way as in the PQRST conditions (Test phase).

Scoring

A scorer blind to the aim of the study and to the experimental hypotheses evaluated, for each prose passage, the frequency of passage units recalled correctly and the frequency of questions answered correctly. The scorer was instructed to consider an answer, or a passage unit, correct when it conveyed the relevant information completely and unambiguously, no matter whether verbatim or not.

Results

Six dependent variables were considered: the frequency of passage units recalled immediately after the study phase and after the delay, and the frequency of correct answers given to the four questions, both immediately and after the delay. For the PQRST-Self condition, we also evaluated the frequency of correct answers given to the other-generated questions. In all cases, the variables were distributed normally (Komolgorov–Smirnov $p > 0.20$ in all cases) and were analyzed with parametric tests.

Free Recall

An analysis of variance (ANOVA) on free recall rates with Test (immediate, delayed) and Condition (PQRST-Other, PQRST-Self, Standard) as within-subject factors showed a significant effect of Test [$F(1,6) = 11.72$, $p = 0.01$], such that participants recalled more units at the immediate compared to the delayed test, and a significant effect of Condition [$F(2,12) = 7.71$, $p = 0.007$]. *Post hoc* Newmann–keuls tests showed that patients recalled more units in the PQRST-Other condition and in the PQRST-Self condition compared to the Standard condition ($p < 0.05$ in both cases), with no difference between the two PQRST conditions ($p = 0.95$; see **Figure 1**). The Condition × Test interaction was not significant ($p = 0.82$).

Frequency of Correct Answers

Similar results were found on the ability to answer questions about the texts. The ANOVA on the frequency of correct answers with Test and Condition as factors showed a significant effect of Test [$F(1,6) = 6.88$, $p = 0.04$], such that correct answers were

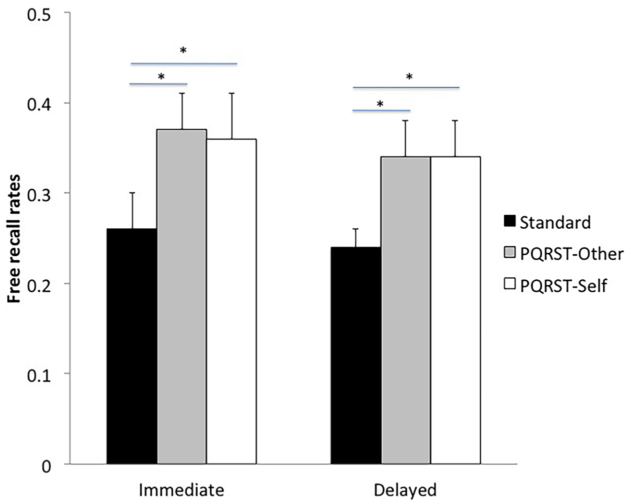


FIGURE 1 | Free recall rates by encoding condition (Standard, PQRST-Other, PQRST-Self) and test (immediate, delayed). Bars represent the SE of the mean. *$p < 0.05$.

more frequent immediately after study than after a delay, and a significant effect of Condition [$F(2,12) = 27.73$, $p = 0.000032$]. *Post hoc* tests showed that patients answered more questions in the PQRST-Other condition and in the PQRST-Self condition compared to the Standard condition ($p < 0.0003$ in both cases), with no difference between the two PQRST conditions ($p = 0.79$) (see **Figure 2**). The Condition × Test interaction was not significant ($p = 0.57$).

We also ran the same ANOVA using the frequency of correct answers to the other-generated questions also for the PQRST-Self condition. There was a significant effect of Condition [$F(2,12) = 15.65$, $p = 0.0005$], which was qualified by a Condition X Test interaction [$F(2,12) = 5.62$, $p = 0.02$]. *Post hoc* tests

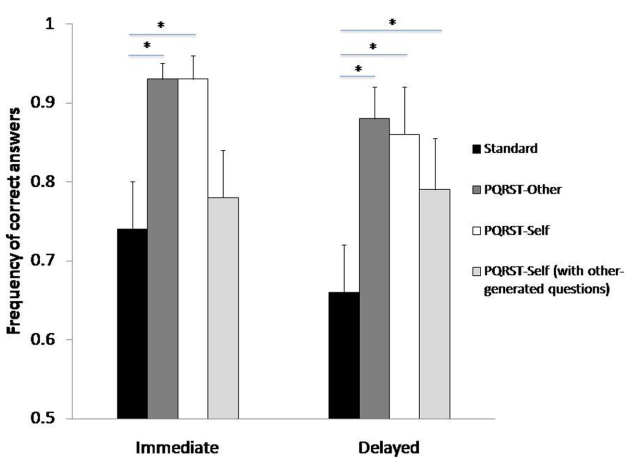


FIGURE 2 | Frequency of correct answers by encoding condition (Standard, PQRST-Other, PQRST-Self) and test (immediate, delayed). Bars represent the SE of the mean. *$p < 0.05$.

showed that in the immediate testing session correct answers were more frequent in the PQRST-Other condition compared to the Standard condition ($p < 0.0001$), but there was no difference between the PQRST-Self and the Standard conditions ($p = 0.15$) (see **Figure 2**). However, in the delayed testing session, correct answers were more frequent in both the PQRST-Other and the PQRST-self condition compared to the Standard condition ($p < 0.0004$ in both cases) (see **Figure 2**). The PQRST-Other condition proved more effective than the PQRST-Self condition both immediately and after a delay ($p < 0.006$ in both cases).

Neuropsychological Profile and PQRST Efficacy

In order to shed light on the type of patients that would benefit the most from the PQRST method, and that would benefit differentially from the classic, PQRST-Other method vs. the PQRST-Self method, we ran correlation analyses between patients' results at standard neuropsycological tests and (1) the difference between scores attained in the PQRST-Other condition and the Standard condition, and (2) the difference between scores attained in the PQRST-Other condition and the PQRST-Self condition (in both cases collapsing across immediate and delayed conditions). Given that, in some cases, the variables were non-normally distributed (Komolgorov–Smirnov $p < 0.05$), we run non-parametric correlation analyses.

We first investigated which aspect of patients' neuropsychological profile predicted the degree of improvement in the PQRST-Other vs. Standard condition. We found that the improvement in answering questions about the texts in the PQRST-Other vs. Standard condition correlated negatively with standardized prose recall scores ($r_{Spearman} = -0.76$, $p < 0.05$) and WMS scores ($r_{Spearman} = -0.77$, $p < 0.05$), and the improvement in free recall correlated negatively with semantic fluency ($r_{Spearman} = -0.92$, $p < 0.005$; see **Figure 3A**). Thus, patients with weak memory and executive functioning benefited the most from a well-organized plan to encode new material. We next investigated which aspect of patients' neuropsychological profile predicted performance differences between the PQRST-Other and PQRST-Self conditions. We found that differences in the ability to answer questions in the PQRST-Other vs. PQRST-Self condition correlated negatively with WMS scores ($r_{Spearman} = -0.82$, $p < 0.05$), and differences in free recall correlated negatively with semantic ($r_{Spearman} = -0.89$, $p < 0.01$) and phonemic fluency ($r_{Spearman} = -0.90$, $p < 0.01$; see **Figure 3B**). Thus, in individuals with more preserved memory and executive functioning the PQRST-Self condition tended to be as effective as the PQRST-Other condition.

Discussion

The present study has two main findings. First, it shows that the PQRST method is effective in improving long-term memory in patients with mild memory and executive problems due to prefrontal cortex lesions. Specifically, the PQRST-Other condition, the version of the PQRST method most frequently

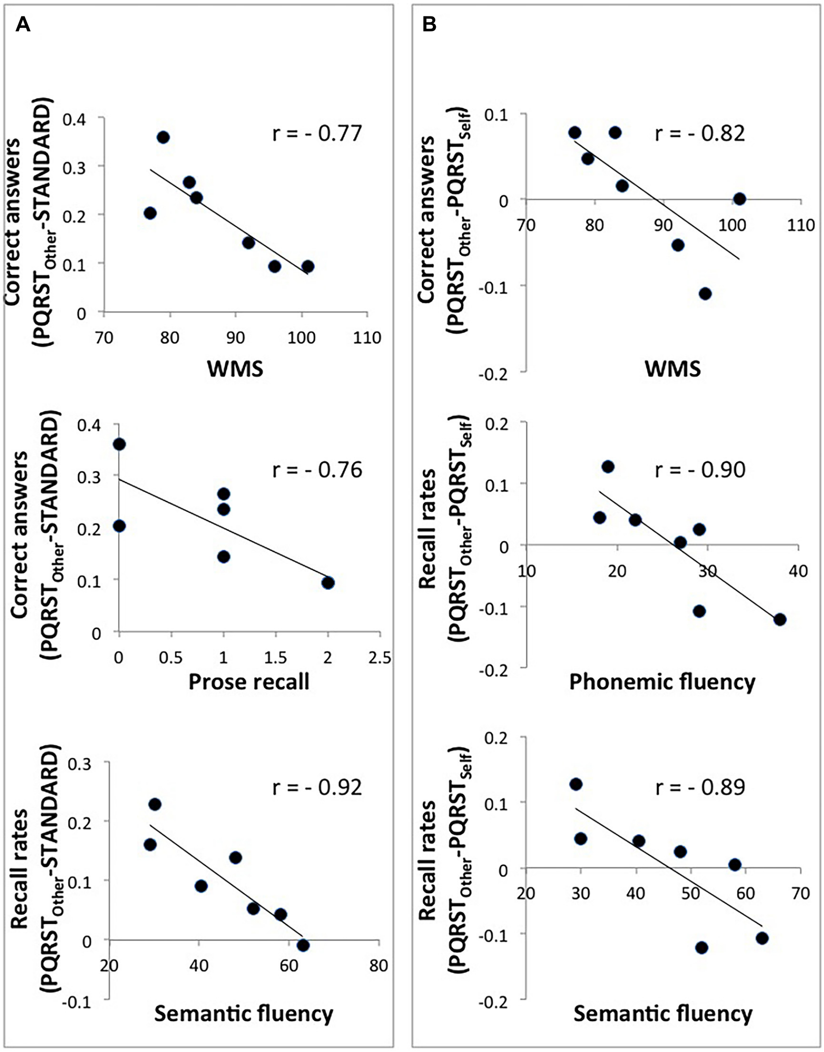


FIGURE 3 | Scatterplots of the correlations between patients' scores at neuropsychological tests and performance differences between the PQRST-Other and the Standard condition (A), and between the PQRST-Other and the PQRST-Self condition (B). $^{*}p < 0.05$.

described in the literature, led to an improvement in both the ability to answer questions about a text and in free recall, both immediately after study as well as after a delay. On average, patients exhibited a 28% improvement in the ability to answer questions and a 40% improvement in free recall. The second main finding of the study is that the same improvement was obtained in the PQRST-Self condition, a modified version of the PQRST procedure in which patients themselves formulated the questions to be used during the study and test phases, indicating that patients can benefit even from alternative forms of the PQRST method that load more heavily on self-initiated processes.

The present results are important in two ways. First, they show that internal methods aimed at optimizing memory encoding can improve memory performance significantly in patients with prefrontal lesions. Importantly, the improvement we observed was not limited to answering questions about a text, which could merely reflect encoding specificity, but extended to free recall, as well as to answering questions different from those that patients had considered at study (PQRST-Self condition, delayed test). This suggests that the PQRST method actually improved patients' ability to encode and store new material.

It has often been hypothesized that patients with prefrontal cortex lesions exhibit problems in learning new information due to an impairment in engaging effective encoding strategies spontaneously (Moscovitch, 1992; Stuss et al., 1994; Gershberg and Shimamura, 1995; Shimamura, 1995; Alexander et al., 2009; Ptak et al., 2010). As discussed earlier, these patients may fail to select the relevant information to attend, and to process and organize it optimally for encoding. For example, an efficient strategy to learn lists of words, a task on which patients in the present study were highly impaired, is to associate them on the basis of their semantic relations, instead of repeating them passively. Making meaningful associations, and processing information semantically, however, require strategy selection and manipulation of information in working memory, which both depend on prefrontal cortex (Shallice and Burgess, 1991; Duncan and Owen, 2000; Baddeley, 2003; Nyberg et al., 2003). Savage et al. (2001) examined the neural bases of spontaneous and directed semantic organization strategies during verbal encoding and found that activity in the inferior prefrontal cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex tracked the degree of semantic clustering observed in free recall. These regions may thus be crucial for the initiation of effective memory strategies (see also Schuck et al., 2015).

The systematic series of encoding operations probed by the PQRST method provided patients with a unique opportunity to process incoming information optimally for learning. Multiple mechanisms may underlie the efficacy of PQRST. First of all, PQRST favors deep (e.g., sematic) encoding of incoming information (Craik, 2002), requiring individuals to scrutinize and interpret the text carefully in order to answer the questions, and to participate actively in the learning process (e.g., Hunt and McDaniel, 1993). Moreover, the PQRST "forces" patients to use the questions as the structure around which they organize encoding. This may help patients to link the different parts of the story to each other, and to appreciate its meaning, again favoring semantic encoding. Notably, questions were available also in the Standard condition, but only the PQRST conditions explicitly demanded their usage. This aspect of the procedure is optimally suited for prefrontal patients, who fail in applying strategies spontaneously. Indeed, the more patients were impaired in memory and executive functions, the more they benefited from application of the PQRST. Another mechanism that may be responsible for memory improvements in the PQRST condition relates to the Question phase being a memory test. Recent research has shown that interpolating the study of prose passages with memory tests can substantially improve learning (Roediger and Butler, 2011), reducing lapses of attention (Pastötter et al., 2011) and mind-wandering (Szpunar et al., 2013). Several prefrontal cortex regions, including ventromedial prefrontal cortex (which was damaged in most our patients), are activated during mind-wandering (Christoff et al., 2009), and may help down-regulate mind-wandering during encoding.

In addition to the (classic) PQRST-Other condition, patients in the present study encoded texts through a modified PQRST-Self condition, in which they formulated the questions on their own. The rationale behind this choice was that, under these encoding instructions, patients would select the passages of the text that were relevant to them, motivating them to inspect the text carefully. Information that is more personally meaningful generally undergoes greater elaboration and organization at encoding, resulting in higher recall rates compared to information that does not have the same relevance (e.g., Klein and Kihlstrom, 1986; Symons and Johnson, 1997). Moreover, the PQRST-Self condition entails self-generation, another factor favoring learning (Slamecka and Graf, 1978). We did not find, however, an advantage of the PQRST-Self over the PQRST-Other condition. One possibility is that because the PQRST-Self condition is more demanding cognitively than the PQRST-Other condition, any advantage caused by self-relevant encoding is offset by the general reduction of cognitive resources in patients. Indeed, patients who performed relatively better in the PQRST-Self condition were those with more preserved executive functioning. Alternatively, given that the ventromedial prefrontal cortex is intimately related to self-processing (e.g., Philippi et al., 2012; D'Argembeau, 2013; Kim and Johnson, 2015), self-relevancy may have not played the strong role we expected in our patients. Interestingly, our data suggest an increased memory advantage from the PQRST-Self condition at the delayed compared to immediate test (i.e., in other-generated questions). Possibly, a brief delay supports the build-up of associations between different parts of the text and with existing semantic structures. Time-dependent memory consolidation effects are tipically found for emotional and rewarding material (Kensinger, 2009), as is self-relevant information. Future studies investigating the effect of different PQRST procedures at delays longer than 10 min, such as hours or days, would help clarify the possible mechanisms through which they operate. It would also be interesting to test the efficacy and neuropsychological basis of PQRST's efficacy in healthy individuals. Unfortunately, a pilot study using our material evinced ceiling effects across conditions in these individuals.

The fact that the two PQRST procedures were equally effective in patients is of great importance for rehabilitation. As anticipated, the ultimate goal of rehabilitation is the ability to transfer the trained skills to other contexts than the laboratory, such as real life. The present finding that a PQRST procedure based on self-formulated questions is effective in ameliorating memory performance suggests that patients with prefrontal lesions could be trained to apply this method in real life, for example to keep track of news or to re-learn some aspects of their autobiography.

Conclusion

We have confirmed that the PQRST is effective to promote new learning in patients with mild memory impairment, and shown that patients may benefit even from alternative versions of the procedure requiring higher levels of self-initiation. Future studies should verify whether patients can generalize the use of PQRST to untrained, and real-life situations. In our laboratory, we are currently investigating whether repeated encoding via the PQRST-Self procedure improves learning of untrained materials.

Acknowledgment

We thank all patients for participating, and Julia Spaniol for her comments on the paper.

References

Alexander, M. P., Stuss, D., and Gillingham, S. (2009). Impaired list learning is not a general property of frontal lesions. *J. Cogn. Neurosci.* 21, 1422–1434. doi: 10.1162/jocn.2009.21094

Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nat. Rev. Neurosci.* 4, 829–839. doi: 10.1038/nrn1201

Baddeley, A. D., and Wilson, B. A. (1994). When implicit learning fails: amnesia and the problem of error elimination. *Neuropsychologia* 32, 53–68. doi: 10.1016/0028-3932(94)90068-X

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–2901. doi: 10.1016/j.neuropsychologia.2007.06.015

Barletta-Rodolfi, C., Gasparini, F., and Ghidoni, E. (2011). *Il Kit del Neuropsicologo Italiano. Società Italiana di Neuropsicologia*. Milano: Edizioni Dynacom.

Barredo, J., Öztekin, I., and Badre, D. (2015). Ventral fronto-temporal pathway supporting cognitive control of episodic memory retrieval. *Cereb. Cortex* 25, 1004–1019. doi: 10.1093/cercor/bht291

Blumenfeld, R. S., and Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist* 13, 280–291. doi: 10.1177/1073858407299290

Bussman-Mork, B. A., Hildebrandt, H., Giesselmann, H., and Sachsenheimer, W. (2000). Treatment of verbal memory disorders: a comparisons of several methods. *Neurol. Rehabil.* 6, 195–204.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., and Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc. Natl. Acad. Sci. U.S.A.* 106, 8719–8724. doi: 10.1073/pnas.0900234106

Ciaramelli, E., and Spaniol, J. (2009). Ventromedial prefrontal damage and memory for context: perceptual versus semantic features. *Neuropsychology* 23, 649–657. doi: 10.1037/a0015937

Craik, F. I. (2002). Levels of processing: past, present, and future? *Memory* 10, 305–318. doi: 10.1080/09658210244000135

Craik, F. I. M., and Lockhart, R. S. (1972). Levels of processing: a framework for memory research. *J. Verbal Learn. Verbal Behav.* 11, 671–684. doi: 10.1016/S0022-5371(72)80001-X

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis. *Front. Hum. Neurosci.* 7:372. doi: 10.3389/fnhum.2013.00372

Doornheim, K., and De Haan, E. H. F. (1998). Cognitive training for memory deficits in stroke patients. *Neuropsychol. Rehabil.* 8, 393–400. doi: 10.1080/713755579

Duncan, J., and Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* 23, 475–483. doi: 10.1016/S0166-2236(00)01633-7

Fletcher, P. C., and Henson, R. N. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124, 849–881. doi: 10.1093/brain/124.5.849

Franzen, K., Roberts, M. A., Schmits, D., Verduyn, W., and Manshadi, F. (1996). Cognitive rehabilitation in pediatric traumatic brain injury. *Child Neuropsychol.* 2, 176–184. doi: 10.1080/09297049608402250

Gershberg, F. B., and Shimamura, A. P. (1995). Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia* 33, 1305–1333. doi: 10.1016/0028-3932(95)00103-A

Gilboa, A., and Moscovitch, M. (2002). "The cognitive neuroscience of confabulation: a review and a model," in *The Handbook of Memory Disorders*, eds A. D. Baddeley, M. D. Kopelman, and B. A. Wilson (New York, NY: Wiley), 315–342.

Harris, J. E. (1992). "Ways to help memory," in *Clinical Management of Memory Problems*, eds B. A. Wilson and N. Moffat (London: Chapman & Hall), 59–85. doi: 10.1007/978-1-4899-4523-5_3

Hunt, R. R., and McDaniel, M. A. (1993). The enigma of organization and distinctiveness. *J. Mem. Lang.* 32, 421–445. doi: 10.1006/jmla.1993.1023

International Committee of Medical Journal Editors. (1991). Style matters: statements from the Vancouver group. *Br. Med. J.* 302, 1194. doi: 10.1136/bmj.302.6786.1194

Jones, M. K. (1974). Imagery as a mnemonic aid after left temporal lobectomy: contrast between material specific and generalized memory disorders. *Neuropsychologia* 12, 21–30. doi: 10.1016/0028-3932(74)90023-2

Kaschel, R., Della Sala, S., Cantagallo, A., Fahlbock, A., Laaksonen, R., and Kazen, M. (2002). Imagery mnemonics for the rehabilitation of memory: a randomised group controlled trial. *Neuropsychol. Rehabil.* 12, 127–153. doi: 10.1080/09602010143000211

Kensinger, E. A. (2009). Remembering the details: effects of emotion. *Emot. Rev.* 1, 99–113. doi: 10.1177/1754073908100432

Kim, K., and Johnson, M. K. (2015). Activity in ventromedial prefrontal cortex during self-related processing: positive subjective value or personal significance? *Soc. Cogn. Affect. Neurosci.* 10, 494–500. doi: 10.1093/scan/nsu078

Klein, S. B., and Kihlstrom, J. F. (1986). Elaboration, organization, and the self-reference effect in memory. *J. Exp. Psychol. Gen.* 115, 26–38. doi: 10.1037/0096-3445.115.1.26

Kopelman, M. D. (2002). Disorders of memory. *Brain* 125, 2152–2190. doi: 10.1093/brain/awf229

Kuhl, B. A., Dudukovic, N. M., Kahn, I., and Wagner, A. D. (2007). Decreased demands on cognitive control reveal the neural processing benefits of forgetting. *Nat. Neurosci.* 10, 908–914. doi: 10.1038/nn1918

Moffat, N. (1992). "Strategies of memory therapy," in *Clinical Management of Memory Problems*, eds B. A. Wilson and N. Moffat (London: Chapman & Hall), 86–119. doi: 10.1007/978-1-4899-4523-5_4

Moscovitch, M. (1992). Memory and working with memory: a component process model based on modules and central systems. *J. Cogn. Neurosci.* 4, 257–267. doi: 10.1162/jocn.1992.4.3.257

Nyberg, L., Marklund, P., Persson, J., Cabeza, R., Forkstam, C., Petersson, K. M., et al. (2003). Common prefrontal activations during working memory, episodic memory, and semantic memory. *Neuropsychologia* 41, 371–377. doi: 10.1016/S0028-3932(02)00168-9

Otten, L. J., Henson, R. N., and Rugg, M. D. (2001). Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. *Brain* 124, 399–412. doi: 10.1093/brain/124.2.399

Pastötter, B., Schicker, S., Niedernhuber, J., and Bäuml, K.-H. T. (2011). Retrieval during learning facilitates subsequent memory encoding. *J. Exp. Psychol. Learn. Mem. Cogn.* 37, 287–297. doi: 10.1037/a0021801

Philippi, C. L., Duff, M. C., Denburg, N. L., Tranel, D., and Rudrauf, D. (2012). Medial PFC damage abolishes the self-reference effect. *J. Cogn. Neurosci.* 24, 475–481. doi: 10.1162/jocn_a_00138

Ptak, R., der Linden, M. V., and Schnider, A. (2010). Cognitive rehabilitation of episodic memory disorders: from theory to practice. *Front. Hum. Neurosci.* 14:57. doi: 10.3389/fnhum.2010.00057

Roediger, H. L. III, and Butler, A. C. (2011). The critical role of retrieval practice in long-term retention. *Trends Cogn. Sci.* 15, 20–27. doi: 10.1016/j.tics.2010.09.003

Savage, C. R., Deckersbach, T., Heckers, S., Wagner, A. D., Schacter, D. L., Alpert, N. M., et al. (2001). Prefrontal regions supporting spontaneous and directed application of verbal learning strategies: evidence from PET. *Brain* 124, 219–231. doi: 10.1093/brain/124.1.219

Schuck, N. W., Gaschler, R., Wenke, D., Heinzle, J., Frensch, P. A., Haynes, J. D., et al. (2015). Medial prefrontal cortex predicts internally driven strategy shifts. *Neuron* 86, 331–340. doi: 10.1016/j.neuron.2015.03.015

Shallice, T., and Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain* 114, 727–741. doi: 10.1093/brain/114.2.727

Shimamura, A. P. (1995). Memory and the prefrontal cortex. *Ann. N. Y. Acad. Sci.* 769, 151–159. doi: 10.1111/j.1749-6632.1995.tb38136.x

Slamecka, N. J., and Graf, P. (1978). The generation effect: delineation of a phenomenon. *J. Exp. Psychol. Hum. Learn. Mem.* 4, 592–604. doi: 10.1037/0278-7393.4.6.592

Spinnler, H., and Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 8(Suppl. 8), 1–120.

Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L., and Pogue, J. (1994). Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 8, 355–373. doi: 10.1037/0894-4105.8.3.355

Symons, C. S., and Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol. Bull.* 121, 371–394. doi: 10.1037/0033-2909.121.3.371

Szpunar, K. K., Khan, N. Y., and Schacter, D. L. (2013). Interpolated memory tests reduce mind wandering and improve learning of online lectures. *Proc. Natl. Acad. Sci. U.S.A.* 110, 6313–6317. doi: 10.1073/pnas.1221764110

Tulving, E., and Thomson, D. M. (1973). Encoding specificity and retrieval processes in episodic memory. *Psychol. Rev.* 80, 352–373. doi: 10.1037/h0020071

Van der Linden, M., and Van der Kaa, M. (1989). "Reorganization therapy for memory impairments," in *Cognitive Approaches in Neuropsychological Rehabilitation*, eds X. Seron and G. Deloche (New York, NY: Lawrence Erlbaum Associates), 105–158.

Wechsler, D. (1945). *The Wechsler Memory Scale*. New York, NY: Psychological Corporation.

Westmacott, R., and Moscovitch, M. (2003). The contribution of autobiographical significance to semantic memory. *Mem. Cogn.* 31, 761–774. doi: 10.3758/BF03196114

Wilson, B. A. (1987). *Rehabilitation of Memory*. New York, NY: The Guilford Press.

Wilson, B. A. (2009). *Memory Rehabilitation: Integrating Theory and Practice*. New York, NY: The Guilford Press.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

CASE REPORT
published: 05 January 2016
doi: 10.3389/fnbeh.2015.00332

The Effects of Short-Lasting Anti-Saccade Training in Homonymous Hemianopia with and without Saccadic Adaptation

*Delphine Lévy-Bencheton[1†], Denis Pélisson[1], Myriam Prost[1,2], Sophie Jacquin-Courtois[1,3,4], Roméo Salemme[1], Laure Pisella[1] and Caroline Tilikete[1,2,3]**

[1] Neuroscience Research Center – Institut National de la Santé et de la Recherche Médicale U 1028 – Centre National de la Recherche Scientifique UMR 5292, Bron, France, [2] Unité de Neuro-ophtalmologie, Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Bron, France, [3] University Lyon 1, Lyon, France, [4] Hospices Civils de Lyon, Hôpital Henry Gabrielle, Saint Genis-Laval, France

OPEN ACCESS

Edited by:
Katiuscia Sacco,
University of Turin, Italy

Reviewed by:
Radek Ptak,
University Hospital Geneva,
Switzerland
Olivier A. Coubard,
CNS-Fed, France

***Correspondence:**
Caroline Tilikete
caroline.tilikete@inserm.fr

†Present Address:
Delphine Lévy-Bencheton,
Queensland Brain Institute, The University of Queensland, St. Lucia, QLD, Australia

Received: 16 March 2015
Accepted: 19 November 2015
Published: 05 January 2016

Citation:
Lévy-Bencheton D, Pélisson D, Prost M, Jacquin-Courtois S, Salemme R, Pisella L and Tilikete C (2016) The Effects of Short-Lasting Anti-Saccade Training in Homonymous Hemianopia with and without Saccadic Adaptation. Front. Behav. Neurosci. 9:332. doi: 10.3389/fnbeh.2015.00332

Homonymous Visual Field Defects (HVFD) are common following stroke and can be highly debilitating for visual perception and higher level cognitive functions such as exploring visual scene or reading a text. Rehabilitation using oculomotor compensatory methods with automatic training over a short duration (∼15 days) have been shown as efficient as longer voluntary training methods (>1 month). Here, we propose to evaluate and compare the effect of an original HVFD rehabilitation method based on a single 15 min voluntary anti-saccades task (AS) toward the blind hemifield, with automatic sensorimotor adaptation to increase AS amplitude. In order to distinguish between adaptation and training effect, 14 left- or right-HVFD patients were exposed, 1 month apart, to three trainings, two isolated AS task (Delayed-shift and No-shift paradigm), and one combined with AS adaptation (Adaptation paradigm). A quality of life questionnaire (NEI-VFQ 25) and functional measurements (reading speed, visual exploration time in pop-out and serial tasks) as well as oculomotor measurements were assessed before and after each training. We could not demonstrate significant adaptation at the group level, but we identified a group of nine adapted patients. While AS training itself proved to demonstrate significant functional improvements in the overall patient group, we could also demonstrate in the sub-group of adapted patients and specifically following the adaptation training, an increase of saccade amplitude during the reading task (left-HVFD patients) and the Serial exploration task, and improvement of the visual quality of life. We conclude that short-lasting AS training combined with adaptation could be implemented in rehabilitation methods of cognitive dysfunctions following HVFD. Indeed, both voluntary and automatic processes have shown interesting effects on the control of visually guided saccades in different cognitive tasks.

Keywords: compensatory training, lateral homonymous hemianopia, reading, saccadic adaptation, visual exploration

INTRODUCTION

Homonymous Visual Field Defects (HVFDs) refers to binocular deficits of lateral visual field, involving either half field (Homonymous Hemianopia) or quarter field (Homonymous Quandranopia). If the deficit persists after 6–8 months following a stroke, it is considered as a chronic visual disorder (Hier et al., 1983; Zhang et al., 2006). Such patients keep having difficulties in high-level cognitive functions such as reading (Zihl, 1995a) or exploring a visual scene (Zihl, 1995b). Disorganized patterns of eye movements might also contribute to the functional problems (Kerkhoff et al., 1992). Compensatory eye-movement strategies can spontaneously take place with time (Zangemeister et al., 1995; Pambakian et al., 2000) but rarely allow patients to reach healthy subjects' performance (Machner et al., 2009). Therefore, during the last decades many rehabilitation techniques have been developed. Among them, the compensatory method, aiming at facilitating large saccades into the blind hemifield in order to bring targets in the normal hemifield, is mainly recommended by experts (Bouwmeester et al., 2007).

Top-down strategy, based on explicit instructions and voluntary saccade training, has demonstrated functional improvements accompanied by oculomotor changes in the visual exploration (Kerkhoff et al., 1994; Zihl, 1995b) or reading (Zihl, 1995a) tasks. However, improvements are usually restricted to the trained ability and do not transfer to other tasks (Schuett et al., 2012). Furthermore, this strategy, where cognitive control is required to improve performance, requires repeated training sessions over months.

Bottom-up strategy relies on implicit oculo-motor training via sensory stimulation. Using a combination of auditory and visual stimuli (Passamonti et al., 2009; Keller and Lefin-Rank, 2010) or creating an optokinetic nystagmus thanks to presentation of a right-to-left moving text (Spitzyna et al., 2007), this strategy has already demonstrated promising results, with a transfer to both reading and visual exploration tasks, with a lower number of training sessions. A protocol combining visual pursuit and target jump toward the blind field has even shown to enhance functional performance following a single 30 min training (Jacquin-Courtois et al., 2013). Therefore, bottom-up strategy represents potentially more efficient and less costly rehabilitation of HVFDs.

Saccadic adaptation has been used for decades as a tool to explore plasticity mechanisms in animal models and humans (see Hopp and Fuchs, 2004; Pélisson et al., 2010 for reviews). It can be induced when subjects perform a series of saccade toward a visual target, which is shifted during the movement, producing a systematic post-saccadic error, which simulates the visual consequence of inaccurate saccades (McLaughlin, 1967). When the target is shifted away simulating short saccades, automatic corrective saccades are elicited. The repetition of such post-saccadic error signals over hundreds of trials is enough to implicitly trigger plasticity mechanisms increasing the amplitudes of saccades. This saccadic adaptation procedure could therefore represent an efficient bottom-up rehabilitation method in order to increase the amplitude of saccades made toward the blind field in HVFD patients. However, since in HVFD patients the target cannot be presented in the blind hemifield, we choose to apply the above procedure to an anti-saccade (AS) task in which subjects have to perform a saccade toward the direction opposite (blind hemifield) to the hemifield where the visual target is presented (healthy hemifield), but with the same amplitude (Hallett, 1978). We recently described in normal subjects that a version of this task with an outward target shift (more eccentrically) occurring at the completion of the AS is capable of adaptively increasing the amplitude of anti-saccades (Lévy-Bencheton et al., 2013).

The objective of this study was to test the effects of this short-lasting saccadic training (15 min), in which we take advantage of the oculo-motor plasticity mechanisms of visuo-motor adaptation in the context of voluntary AS training. In order to distinguish between the effects of the AS training (top–down method since AS involve the inhibition of the automatic saccade toward the peripheral visual target) and of the visuo-motor adaptation elicited by specific feedback target presentation (bottom-up method), 14 left- and right-HVFD patients were randomly submitted to three different 15 min AS tasks separated by 4 or 5 weeks, only one being designed to trigger outward oculo-motor adaptation of saccades made toward the blind field. Immediate re-appearance of the saccade target systematically shifted further away with respect to eye landing position at the saccade offset is known to trigger implicitly plasticity mechanisms increasing saccade amplitude (Adaptation), contrary to delayed or un-shifted re-appearance of the saccade target (Fujita et al., 2002; Lévy-Bencheton et al., 2013) which correspond to control conditions to test for the specificity of the effects of bottom-up adaptation mechanisms.

Visual Exploration (Pop-out and Serial) and Reading tasks were performed immediately before and after each AS task, as well as a Visual Function Questionnaire, to evaluate the functional and oculomotor effects of the three different trainings.

MATERIALS AND METHODS

Participants

Seventeen patients with a chronic HVFD after a stroke were asked to attend the inclusion visit (V0). Each patient underwent neurological and ophthalmological clinical examinations and assessment of the 30° central visual field (automated static system, Metrovision®, Pérenchies, France). A neuropsychological assessment of unilateral spatial neglect was performed during V0, including 10 trials of 20 cm line bisection test (Harvey and Milner, 1995), a stars cancelation test from the Behavioral Inattention Test (Halligan et al., 1991), a spontaneous daisy drawing and a clock test. None of them were under medications altering cognitive functions required for the task. All patients signed the written informed consent to participate to the study. Approval of all procedures was received from the National French ethical committee on human experimentation (Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) and Comité de Protection des Personnes (CPP) Sud-Est III), in agreement with French law (March 4, 2002) and the Declaration of Helsinki (n° 2008-057B).

According to inclusion and exclusion criteria (**Table 1**) checked during the inclusion visit, 14 patients participated to the study (mean age 57 ± 10.51 y.o.; range 38–78; nine men and five women). Eight patients presenting a right-HVFD, six a left-HVFD, were included at least 6 months following an ischemic stroke (**Figure 1**). Clinical data of the patients are summarized in **Table 2**.

TABLE 1 | Inclusion and exclusion criteria assessed at the inclusion visit (V0).

Inclusion criteria	Exclusion criteria
✓ Patient with right- or left-HVFD	✓ Visuo-spatial neglect
✓ Age: 18–80 years (included)	✓ Ophthalmologic (monocular visual acuity ≤4/10; strabismus, diplopia; ocular instability; nystagmus; maculopathy; glaucoma; retinopathy; ongoing orthoptic rehabilitation)
✓ Etiology: ischemic stroke	✓ Neurologic (understanding disorder; degenerative neurologic disorder; epilepsia; severe handicap not allowing sitting position for 2 h or concentrate for 30 min)
✓ Post stroke delay: at least 6 months	✓ Not French reader
✓ Single lesion demonstrated on MRI	✓ Non-stabilized medical affection
✓ Far and near visual acuity ≥5/10	✓ Pregnancy
✓ Understanding the experimental recommendations	✓ Patient unable to sign consent
✓ Sitting position possible for 2 h	
✓ Patient consenting to the study	

Study Design

After the inclusion visit V0, the patient came for three successive visits (V1, V2, and V3) each separated by 4–5 weeks. During each visit, one out of the three computerized-training (Delayed-shift, Adaptation, No-shift) was tested. Delayed-Shift training was systematically performed in V1, so that each patient could learn how to proceed with the training task (more details below). During V0, within each group of patient with right- or left-HVFD and with or without macular sparing, the patients were randomly attributed the training order for V2 and V3 (Adaptation or No-Shift training) (**Figure 2**). A fourth follow-up visit (V4) was organized after V3. The whole duration of the protocol for a given patient was between 14 and 21 weeks. Each visit started with the NEI-VFQ 25 (National Eye Institute 25-Item Visual Function Questionnaire, 2000) systematically assessed by a blind investigator. The three training visits (V1, V2, and V3) included the training period and immediate pre- and post-visual exploration and reading phases. A last assessment of NEI-VFQ 25, visual exploration and reading performance, and visual field was performed during the last visit (V4).

Eye Movement Recording and Analysis

Horizontal and vertical eye positions were continuously recorded during visual exploration, reading and training, using an infrared

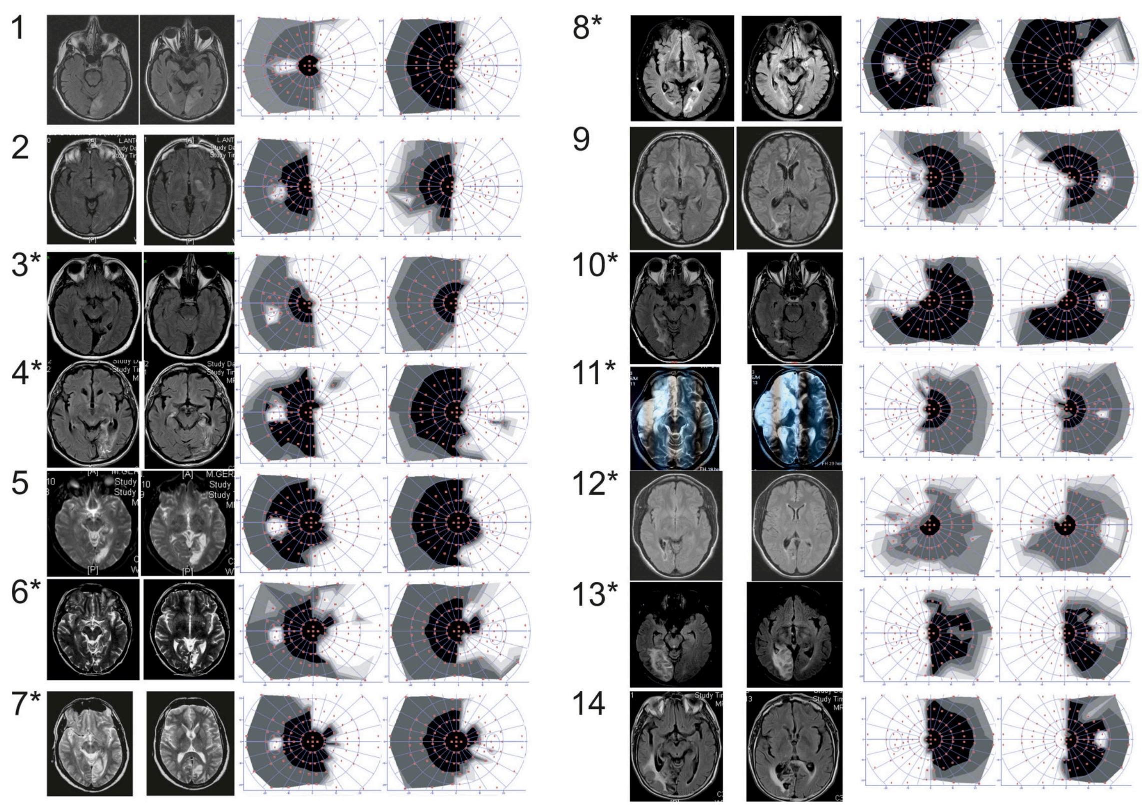


FIGURE 1 | Patients number. Patients with (*) or without (no *) positive slope, MRI (either T2 or FLAIR axial sequences) and 30° central visual field (automated static system, Metrovision®, Pérenchies, France) in the overall group of patients. White part of the visual field refers to the blind part of the visual field.

Eye-Tracker system (Cambridge Research System, Cambridge, UK). The infrared camera was mounted above a chin-rest and allowed high frequency (250 Hz) acquisition of the eye images which were reflected by a 45° tilted mirror located in front of the subject. The patient was seated in front of a computer screen (140 Hz vertical refresh rate), his head maintained by the chin-rest at 57 cm from the screen. Patient's eye position was calibrated using a nine-point grid at the beginning of each session (or anytime he/she moved the head).

TABLE 2 | Clinical data of the patients.

Patients	Sex	Age	Delay in months	Cerebral artery territory
1	M	67	30	Posterior
2	M	57	48	Middle
3	F	44	78	Posterior
4	M	66	12	Posterior
5	M	63	84	Posterior
6	F	52	180	Posterior
7	M	59	120	Posterior
8	M	78	7	Posterior
9	M	53	36	Posterior
10	M	60	138	Posterior
11	F	50	108	Middle
12	F	38	96	Posterior
13	F	50	72	Posterior
14	M	67	12	Posterior

Patients 1–8 represent right-HVFD and patients 9–14 represent left-HVFD following a left and right hemisphere lesion, respectively.

All horizontal and vertical saccades were analyzed offline using a laboratory-developed program under Matlab version 7.8 (Mathworks, MA, USA) and this automatic analyze was manually checked and corrected by the experimenter if needed.

Pre- and Post-Phases

Visual Exploration Tasks

For both *Pop-out and Serial exploration* tasks, 63 images (20° horizontal, 15° vertical) representing black-edges balloons on a white background were successively presented on the screen, with a variable amount of stimuli (12, 24, or 48). Patient was asked to find a target among distracters, and pushed a button as soon as he found the target or another button if no target was found. The target was present in 20 trials and absent in one trial per stimulus difficulty (amount of distracters). In the Pop-out exploration task, the patient had to find a balloon with a string among balloons without strings (**Figures 3A,B**). In the Serial exploration task, he had to find the only balloon without string among balloons with strings (**Figures 3C,D**; Morris et al., 2004).

Reading Task

Two texts were successively presented to the patient. Each text was extracted from French newspaper, written in black letters on a white background, in Times New Roman font, size 30, justified (**Figure 3E**). Sets of three letters spanned 2° of visual angle. Each text had similar number of words (85–90 words per text), and had the same neutrality in order to avoid emotional bias. The patient was asked to silently read each text at his own speed, and had to push a button as soon as he finished reading. After reading the two texts, comprehension was confirmed by asking the patients to verbally summarize their content. A new text was presented at each session and visit in order to avoid any learning effect.

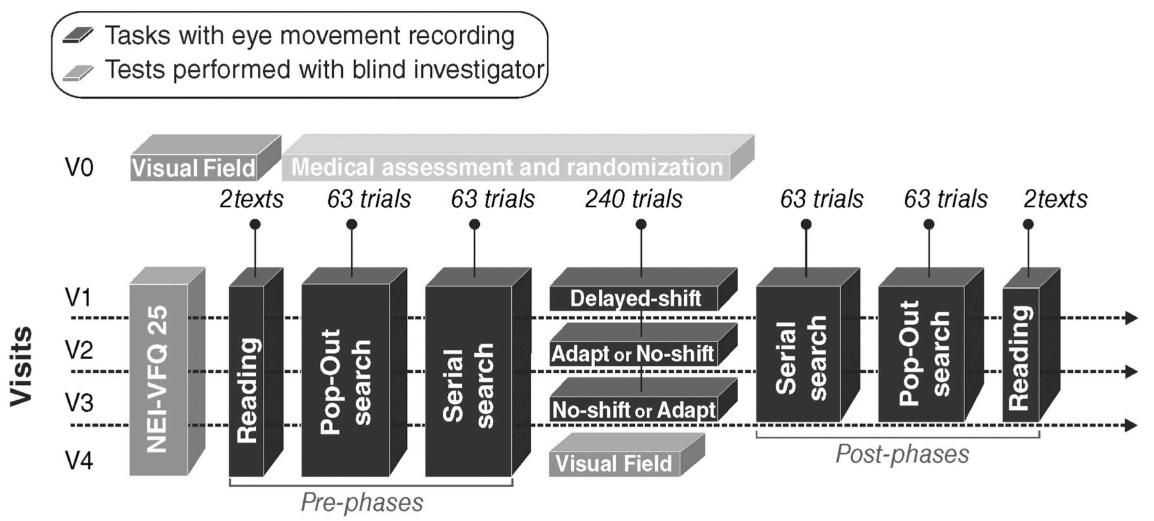


FIGURE 2 | Study design. Each patient came first for an inclusion visit (V0) and then four times: three visits with a training (V1, V2, and V3) plus a follow-up visit (V4). V1 occurred 1–6 weeks after V0 and an interval of 4 or 5 weeks spanned between each of the four following visits. Black blocks correspond to the eye movements recording tasks. Gray blocks correspond to tests performed with a blind investigator. Light gray block corresponds to the medical assessment and the randomization of training.

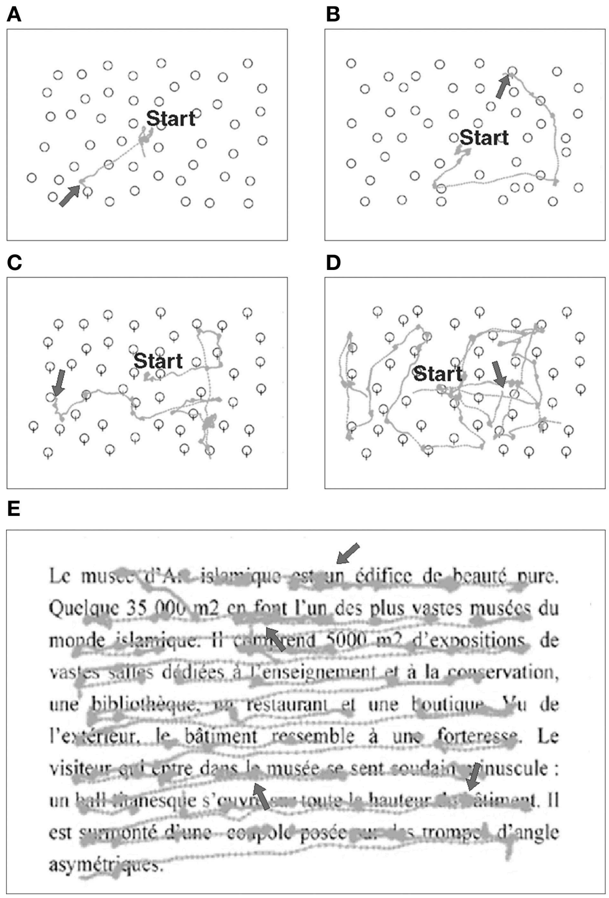


FIGURE 3 | Examples of eye movement recordings during visual exploration and reading tasks in a patient (#8) with right-HVFD. Gray traces represent raw eye movements performed by the patient. In the Pop-out **(A,B)** and Serial **(C,D)** exploration tasks, arrow signals the endpoint of the saccade made to the target. When the target is in the healthy hemifield (**A,C**) fewer exploration saccades are made as compared to when the target is in the blind hemifield (**B,D**). In the reading task **(E)**, arrows point to the typical oculomotor deficits of right HVFD patients, i.e., smaller saccades with higher rate of fixations.

NEI-VFQ 25

The 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ 25) attests the quality of life (QOL) of patients with 25 different items focusing on vision and grouped in 12 subscales including one single-item subscale focusing on general health. Each subscale is scored within a 100-point scale with 100 indicating no difficulty and 0 indicating the worst difficulties. A composite score—mean score of all subscales except the general health item—is used.

Training

The training consisted of three different anti-saccades (AS) training: one with (Adaptation) and two without (Delayed-shift and No-shift) saccadic adaptation (**Figure 4**). More details of the general procedure and on these three trainings can be found in a previous study (Lévy-Bencheton et al., 2013).

Task Common to the Three Trainings

Each patient gazed at a central red cross used as a Fixation Point (FP). After a random time (range: 1100–1500 ms), a peripheral target was presented in the healthy hemifield, on the horizontal meridian, randomly at 6°, 9°, or 12° lateral to the FP (overlap paradigm). The patient was instructed to execute an AS in the direction opposite to the target (thus in the blind hemifield), with equivalent amplitude. He had to react within a delay of 1400 ms after peripheral target presentation, which remains on the screen until detection of the saccade. The timing could be adapted to the patient's ability, usually by increasing the delay if the patient was too slow. Thanks to a gaze-contingent paradigm, the appearance and disappearance of stimuli on the screen were strictly controlled: as soon as the AS was detected, FP and peripheral target were extinguished by the software. Upon completion of the AS a "feedback" target (FT) was presented either at the mirror position of the peripheral target (No-Shift) or shifted 10% outward with respect to the executed saccade (i.e., shifted in the blind hemifield; Adaptation and Delayed-shift) depending on the actual training (see following paragraphs). To re-inforce saccade accuracy, a spatio-temporal criteria had to be met in order to present the feedback target: the saccade has to reach at least 90% of the mirror peripheral target distance (spatial threshold) within 600 ms (temporal threshold) after the initiation of the saccade following FP and target disappearance (more details in Lévy-Bencheton et al., 2013). If succeeded, a short and high-pitched "success" sound was presented to the subject. If the spatio-temporal criteria were not fulfilled, a longer low-pitched "error" sound occurred and the feedback target was not presented. After completion of the AS, patient was instructed to shift his gaze back to the center of the screen in preparation to the next trial. A total of 240 trials (80 for each target position) was presented. In case of excessive failure trials (above 20%), the total amount of presented trials was increased up to 300. Each training lasted around 15–20 min.

Differences between Training

Only parameters concerning the feedback target were varied between the three trainings (**Figure 4**). For the adaptation training, the feedback target was systematically presented with an offset, with respect to final eye position, in the direction of increasing eccentricity (outward) and with an amount equal to 10% of the actual size of eye displacement (**Figure 4B**). This feedback target was turned on at the end of the anti-saccade without any delay (0 ms). For the delayed-shift training, the feedback target was presented at the offset location but delayed from the end of the anti-saccade by 800 ms (**Figure 4A**). For the No-shift training, the feedback target was presented without any delay but at a location, which corresponded to the mirror target position (**Figure 4C**).

Data Analysis

Computerized-tests (Visual exploration, reading) were submitted to two different kind of measurements. The *functional and oculomotor measures* represent parameters defining the subject's performance in the different tasks excluding eye movements (i.e., time needed to perform the visual exploration and reading tasks,

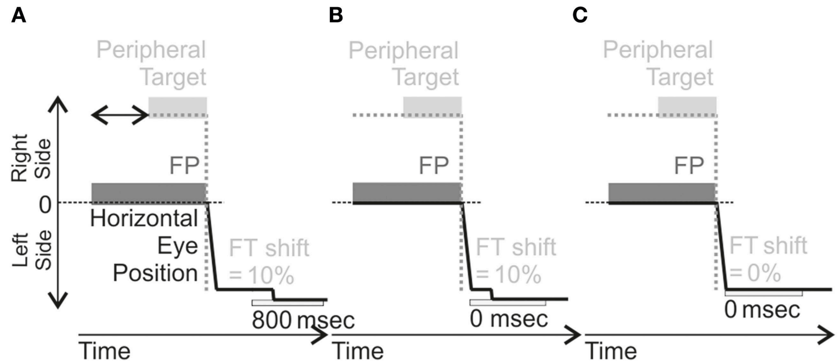


FIGURE 4 | Schema of AS training in the different training. These illustrations are for Left-HVFD patients (leftward AS elicited by a target in the right visual field). For each training, the Fixation Point (FP) is first presented, followed by a peripheral target appearing between 1100 and 1500 ms (horizontal black arrow represented in A) after FP presentation, located on the right. In the Delayed-Shift training (**A**), the feedback target (FT) is presented 800 ms after AS completion at a location shifted outward by 10% of the anti-saccade amplitude. In the Adaptation training (**B**), the FT is also presented at the shifted location (same 10% offset) but at the time of anti-saccade completion (0 ms). In the No-Shift training (**C**), the FT is presented without delay from anti-saccade completion (0 ms) but also without offset, i.e., at the mirror position of the peripheral target. For Right-HVFD patients, the training was similar except that the peripheral target was now presented on the left side and anti-saccades performed to the right.

measuring the Reaction time, word per minute, respectively) and parameters defining the subject's performance in the different tasks including eye movements (mean saccadic amplitude, mean fixation duration), respectively. The questionnaire of Quality of Life (NEI-VFQ 25) and the Visual Field were analyzed separately. We present below the main analysis, which specifically tested our hypotheses, and the complementary analyses, which were performed as follow-up when the main analysis provided significant results.

Main Data and Statistical Analyses

Regression slope

The regression slope of the relationship, during all training, between primary saccade gain and trial number was measured for each patient separately, for each target eccentricity (6°, 9°, and 12°) and was then averaged across target eccentricities. To evaluate whether the saccadic gain evolved significantly over the time of training, we performed a one-sample t-test comparison of the averaged regression slopes to the standard value 0.

Predictive independent factors

Individual positive or negative slope during the adaptation training was used as a two levels predictive independent factor in all following functional and oculomotor statistical analysis, to test for the potential effect of gain change during the adaptation training (i.e., plasticity mechanisms). HVFD-side and Macular Spare are two factors, which can influence reading performance (Zihl, 1995a; Trauzettel-Klosinski and Brendler, 1998; Upton et al., 2003). Thus, these last two factors have been added as predictive independent factors in the ANOVAs related to reading.

Visual field

The mean macular threshold and the mean corrected deficit for the two eyes were calculated in each patient, separately for the inclusion visit (V0) and the last visit (V4). Paired t-test was performed to compare the *macular threshold and the mean corrected deficit,* separately, between the first (pre-phase: V0) and last visit (post-phase: V4).

Visual exploration tasks (Pop-out and Serial)

Functional measures. Reaction time (RT, in ms) was calculated for trials with target present as the period elapsing between the presentation of the image on the screen and the response of the patient (press button). A Two-way repeated measures ANOVA was performed on the RT, separately for the Pop-out and Serial exploration tasks, with the following dependent factors: Training (Delayed-Shift/Adaptation/No-shift) and Phase (Pre-phase/Post-phase) with the factor slopes (Positive/Negative) as predictive independent factor.

Oculomotor measures. Mean horizontal amplitude of saccades performed toward the treated-side and non-treated side were calculated over the entire block and averaged for each participant. Mean fixation duration before the forthcoming saccades toward the treated vs. non-treated side (beginning of the forthcoming saccade—ending of the previous saccade) were also calculated for each block and averaged for each patient. Mean horizontal saccadic amplitude and mean fixation duration were submitted to a Three-way repeated measures ANOVA, separately for the Pop-out and Serial exploration tasks, with the following factors: Saccade Direction (Treated/Non-treated side), Training (Delayed-Shift / Adaptation / No-Shift) and Phase (Pre-phase / Post-phase), with the factor slopes (Positive / Negative) as predictive independent factor.

Reading task

Functional measures. Reading time was calculated as the time elapsing between the eye fixating the very first word and the very last word of each text. Reading speed (word per minute) was calculated as the number of words read divided by reading time. A Two-way repeated measures ANOVA was performed on the word per minute (WPM) with the Training and the Phase as dependent factors, with the factor slopes (Positive/Negative) HVFD side (Left-HVFD/Right-HVFD) and macular spare ($<5°/>5°$) as predictive independent factors.

Oculomotor measures. Mean horizontal amplitude of saccades performed toward the treated-side and non-treated side were calculated over the entire text and averaged for each participant. A Three-way repeated measures ANOVA was performed on the mean horizontal saccadic amplitude testing the effect of Training (Delayed-Shift/Adaptation/No-Shift), Saccade Direction (Treated side/Non-treated side) and Phase (Pre-phase/Post-phase). The slopes, HVFD side and macular spare were added as predictive independent factors. Note that here, Treated-side corresponds to leftward return saccades and Non-treated side to rightward reading saccades in left HVFD patients, whereas the opposite is true for right HVFD patients. Note also that for the return saccades, only those from the right-end of a line to the left-start of the next line were taken into account (Zihl, 1995a). Mean fixation duration and numbers of saccades before a forthcoming return saccade vs. a forthcoming reading saccades were also calculated for each text and averaged for each patient. Because of the different nature of the reading (rightward) vs. return (leftward) saccades (i.e., fewer return saccades as compared to the reading saccades, independently of the treated-side) these analysis were performed separately with the factors Training and Phase submitted to a Two-way repeated measures ANOVA excluding the treated-side factor.

NEI-VFQ 25

Composite scores measured during each visit were used to determine the potential effect of training on the patients' quality of life (QOL). Pre-phase scores were determined by the questionnaire at the beginning of the session while the corresponding post-phase scores were determined at the beginning of the next visit 1 month later. A One-way repeated measure ANOVA with four levels (i.e., pre-delayed/baseline, post-delayed, post-adapt and post-no-shift) was performed on the composite score with the dependent factors Training. Additionally, because of the different categories tested in that questionnaire (including reading component) we assessed whether the saccadic training influences the composite score of the NEIVFQ25 questionnaire. For these reasons, we thought relevant to add the slopes, the HVFD side and macular spare as predictive independent factors.

Complementary Data and Statistical Analysis

In case of specific increase of performance immediately after the adaptation training, in functional *or* oculomotor parameters, we performed long-term analyses thanks to paired-*t* tests on the same parameter at 1 month. These long-term analyses compared the immediate post-phase following the adaptation training with the pre-phase at 1 month (visit V3 or V4).

Note that in case of specific *and* simultaneous (functional and oculomotor) increase of performance following the adaptation training, additional analyses were performed on oculomotor parameters such as number of saccades and were also checked at 1 month.

Statistical analyses were performed with the Statistica 10 software (Statsoft, Tulsa, OK). *Post-hoc* Least Significant Difference (LSD) Fischer was performed following a significant interaction in ANOVAs. Significant level was set at $p < 0.05$.

RESULTS

Regression Slope and Adaptation Marker

The slope of the relationship between gain of the anti-saccades and trial number during the three trainings did not differ significantly from zero at the group level, [$t_{(41)} = -0.28$, $p = 0.78$; $t_{(41)} = 1.41$, $p = 0.16$; $t_{(41)} = -1.90$, $p = 0.06$ for the Delayed-shift, Adaptation and No-shift training, respectively]. However, five patients had a negative (range from −0.001118 to −0.000080) and nine patients a positive slope (range from 0.000033 to 0.001294), five of whom had right-HVFD and four left-HVFD. The slope of the relationship between gain of the anti-saccades and trials numbers during the adaptation training differed significantly from zero at a group level, for patients who showed positive slope [$t_{(26)} = 4.65$, $p < 0.01$]. The signed slope of the relationship between gain and trial number during the adaptation training was used as a marker of the efficiency of the outward anti-saccade adaptation for the oculomotor statistical analyses (see Section Materials and Methods) and for the NEI-VFQ 25 questionnaire.

Visual Field

Mean macular threshold and mean corrected deficit did not differ at visit V4 (28.83 and 8.23 dB) as compared to the pre-phase (28.78 and 8.56 dB) [$t_{(13)} = -0.07$, $p = 0.94$ and $t_{(13)} = -1.92$, $p = 0.07$].

Visual Exploration Tasks

Pop-out

Functional measures

Following the Two-way repeated measures ANOVA with the factors Training and Phase, and the factor slopes as predictive independent factor, we observed a significant decrease of the RT following all training [main effect of Phase: $F_{(1, 12)} = 5.17$, $p = 0.04$]. Further, a significant Training × Phase interaction [$F_{(2, 24)} = 3.78$, $p = 0.037$] resulted from a significant decrease of the RT in post-phase [1504.6 ms] relative to the pre-phase [1650.4 ms] for the delayed-shift training only [$p = 0.019$]. Neither the decrease of RT in post-phase for the adaptation training [1473.9 pre-/1380.8 post-] nor the increase in the post-phase for the no-shift training [1436.4 pre-/1504.7 post] were significant ($p = 0.12$ and 0.25, respectively; **Figure 5A**).

Oculomotor measures

Despite a significant interaction between Training × Phase × Slope [$F_{(2, 24)} = 4.76$, $p = 0.018$], following the Three-way repeated measures ANOVA with the factors Training, Phase and Saccade Direction, and the factor slopes as predictive independent factor, there was no significant increase of saccade amplitude during the Pop-out exploration task in the group of patients who demonstrated a positive slope i.e., an increase of anti-saccade amplitude during the adaptation training [$p =$

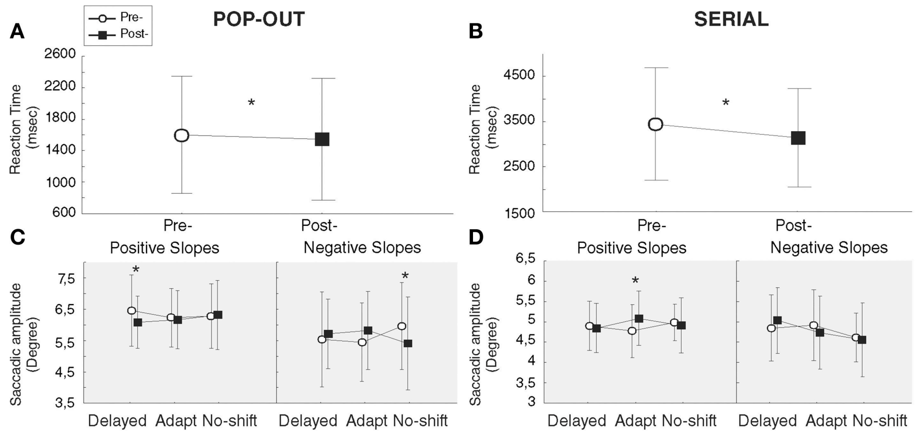


FIGURE 5 | Results of exploration tasks. Functional **(A,B)** and oculomotor (**C,D**, gray background) measures of Pop-out **(A,C)** and Serial **(B,D)** exploration tasks. Bars represent the confident interval at 0.95. Stars represent significant differences between pre- and post-phases revealed by *Post-hoc* LSD Fisher test.

0.70] (**Figure 5C**). The interaction was instead driven by a significant amplitude decrease of saccades following the delayed-shift training for this group [$p = 0.04$] and following the no-shift training for the group in which the adaptation training was inefficient (negative slope) [$p = 0.02$]. These changes were also supported by the three level interaction of the Saccade direction × Training × Phase [$F_{(2, 24)} = 5.68$, $p = 0.009$] showing that the significant amplitude decrease following the delayed-shift training occurs for the treated-side [$p = 0.005$] and for the non-treated-side following the no-shift training ($p < 0.001$). There was no change of fixation duration in either training (Phase effect [$F_{(1, 12)} = 0.08$, $p = 0.77$]; Training × Phase interaction [$F_{(2, 24)} = 3.28$, $p = 0.055$]; **Table 3**).

Serial

Functional measures

Following the Two-way repeated measures ANOVA with the factors Training and Phase, and the factor slopes as predictive independent factor, we observed a main effect of Phase [$F_{(1, 12)} = 20.15$, $p < 0.001$], due to a significant decrease of RT in the post-phase [3148.2 ms] as compared to the pre-phase [3451.4 ms], independently of the training (no interaction; **Figure 5B**). In addition, we found a Training × Slope interaction [$F_{(2, 24)} = 7.28$, $p = 0.003$] in which the group of patients with positive slopes is faster than the group of patients with negative slopes to explore the visual scene in the adaptation [$p = 0.04$] and no-shift [$p = 0.02$] training, independently of the phase.

Oculomotor measures

Three-way repeated measures ANOVA with the factors Training, Phase and Saccade Direction, and the factor slopes as predictive independent factor has been performed and revealed a significant and specific increase of the saccadic amplitude following the adaptation training only, for the patients with positive slopes [$p = 0.003$] (Training × Phase × Slope interaction [$F_{(2, 24)} = 5.69$, $p = 0.009$]; **Figure 5D**). No significant interactions occur for the Saccade direction × Training × Phase [$F_{(2, 24)} = 3.01$, $p = 0.068$] nor the for the Saccade direction × Training × Phase × Slope [$F_{(2, 24)} = 2.97$, $p = 0.07$]. Concerning fixation duration, neither Phase effect nor Training effect nor Training × Phase interaction were demonstrated [$F_{(1,12)} = 1.16$, $p = 0.30$; $F_{(2, 24)} = 1.00$, $p = 0.38$; $F_{(2, 24)} = 2.53$, $p = 0.10$, respectively] (**Table 3**).

Reading

Functional Measures

Two-way repeated measures ANOVA with the factors Training and Phase and the slopes, HVFD-side and Macular spare as predictive independent factors has been performed for the functional measures of the reading task. Analyses of the WPM could not be performed in one patient because we failed to identify the end of the reading due to a lack of eye-tracking signal (see Section Materials and Methods). Reading speed (WPM) of the 13 analyzed patients was significantly increased following the adaptation and the no-shift training ($p = 0.0003$ and 0.002, respectively), yielding a significant Training × Phase interaction [$F_{(2, 10)} = 6.66$, $p = 0.014$]. Additionally, the Training × Phase × HVFD-side interaction [$F_{(2, 10)} = 4.50$, $p = 0.04$] showed that in right-HVFD patients the reading speed increased following each training [125.6–139.5 WPM, $p = 0.03$; 130.5–148.6 WPM, $p = 0.009$; 121.5–142.5 WPM, $p = 0.004$ for Delayed-shift, Adaptation, and No-shift training, respectively], while in left-HVFD patients a specific increase of reading speed from 136.2 to 168 WPM was found after the adaptation training only [$p = 0.001$; $p = 0.1$; $p = 0.1$ for adaptation, delayed-shift, and no-shift training, respectively] (**Figures 6A,B**). Long-term analyses performed on the reading speed of left-HVFD patients at 1 month following the adaptation training visit did not reveal any difference with the initial post-adaptation measure [$t_{(4)} = -2.13$, $p = 0.10$], showing that the beneficial effects remained at long-term.

Oculomotor Measures

Three-way repeated measures ANOVA performed on the oculomotor measures revealed a significant HVFD-side × Saccade direction interaction [$F_{(1, 5)} = 404.61$,

TABLE 3 | Mean fixation duration in ms (±SD) of the forthcoming saccades performed toward the treated- vs. non-treated side in visual exploration and reading tasks.

	Delayed-shift		Adaptation		No-shift	
	Pre-phase	**Post-phase**	**Pre-phase**	**Post-phase**	**Pre-phase**	**Post-phase**
POP-OUT						
Treated-side	213.38	206.28	220.56	196.85	200.31	240.98
	(±38.09)	(±44.57)	(±88.93)	(±82.14)	(±44.64)	(±145.30)
Non-treated side	208.02	199.31	193.81	183.70	195.84	222.09
	(±41.59)	(±45.33)	(±49.57)	(±71.29)	(±45.81)	(±104.18)
SERIAL						
Treated-side	218.83	213.97	223.14	214.24	211.66	235.14
	(±41.70)	(±46.09)	(±76.34)	(±51.33)	(±48.64)	(±103.80)
Non-treated side	220.59	215.65	222.11	215.31	213.09	245.33
	(±53.12)	(±47.97)	(±62.85)	(±48.82)	(±48.90)	(±143.75)
READING (BEFORE RETURN SACCADES)						
Treated-side	206.76	232.88	230.93	228.93	225.40	233.28
(left-HVFD)	(±91.73)	(±102.05)	(±71.11)	(±66.94)	(±102.90)	(±130.42)
Non-treated side	294.53	230.48	271.86	266.61	259.50	275.56
(right-HVFD)	(±118.38)	(±44.98)	(±71.68)	(±86.02)	(±68.72)	(±87.28)
READING (BEFORE READING SACCADES)						
Treated-side	274.87	247.18	271.32	258.95	277.04	263.37
(right-HVFD)	(±61.86)	(±41.45)	(±66.21)	(±61.51)	(±66.23)	(±61.09)
Non-treated side	257.34	270.76	273.82	266.24	252.10	224.72
(left-HVFD)	(±68.87)	(±37.38)	(±82.70)	(±68.95)	(±71.79)	(±33.32)

$p < 0.0001$] led us to perform separate analyses for saccades in the treated-side and those in the non-treated side. Results for the treated-side saccades showed a significant increase of the amplitude of return leftward saccades for the left-HVFD patients with positive slopes following the adaptation training only [$p = 0.001$] [interaction Training × Phase × HVFD-side × Slope [$F_{(2, 10)} = 7.68$, $p = 0.009$] (**Figure 6C**). The absence of difference in the follow-up long-term analysis [$t_{(2)} = -0.93$, $p = 0.45$] suggests that this improvement is still present at 1 month. In addition, in the same patients (left-HVFD patients with positive slopes), we observed a decrease of the number of leftward saccades again specifically following the adaptation training (Training × Phase × HVFD-side × Slope interaction [$F_{(2, 18)} = 6.26$, $p = 0.008$]; **Figure 6G**) and again remaining stable at 1 month [$t_{(2)} = 1.15$, $p = 0.37$]. Mean fixation duration was unchanged both for the return saccades (Main effects, all $p > 0.12$; interactions, all $p > 0.14$) and the reading saccades (Main effects, all $p > 0.53$; interactions, all $p > 0.08$; **Table 3**).

NEIVFQ 25

One-way repeated measures ANOVA revealed a significant improvement of the composite score following the adaptation training (composite score 91.41%) as compared to the baseline pre-delayed-shift training (composite score 73.48%, $p = 0.005$) and post-delayed-shift training (composite score 84.84%, $p = 0.03$) only for the patient presenting a positive slope and having a macular spare superior to 5° [3 levels interaction Training × Macular spare × Slope; $F_{(3, 18)} = 4.99$, $p = 0.01$] (**Figure 7**).

DISCUSSION

In this study, we aimed to test whether a procedure of adaptation of anti-saccades in hemianopic patients could improve their performance in visual exploration, reading and quality of life. To test the specificity of the adaptation component of this procedure, we also designed two control tasks in which subjects simply performed AS without adaptation (Delayed-shift, No-shift). While AS adaptation procedure has been validated in healthy subjects (Lévy-Bencheton et al., 2013), only nine among 14 patients showed the expected increase of AS gain (positive slope). Overall, we found that all three trainings significantly improved visual exploration (decreased RT) in the entire group of patients. In addition, all training improved the reading speed in right-HVFD patients. These functional improvements were not associated to a training-specific increase in saccade amplitude. We, however, found effects specific to the adaptation training, in patients showing a positive slope. First, a significant improvement of reading speed in left-HVFD patients, associated with specific changes of leftward (return) saccades (increased amplitude and decreased number). These effects of the brief adaptation training in left-HVFD patients were maintained 1 month later. Second, an increase of the saccadic amplitude was observed in the Serial exploration task for patients who increased their AS amplitude during the adaptation training. Finally, patients with a macular spare superior to 5° and a positive slope demonstrated a specific improvement of the visual quality of life score following the adaptation training.

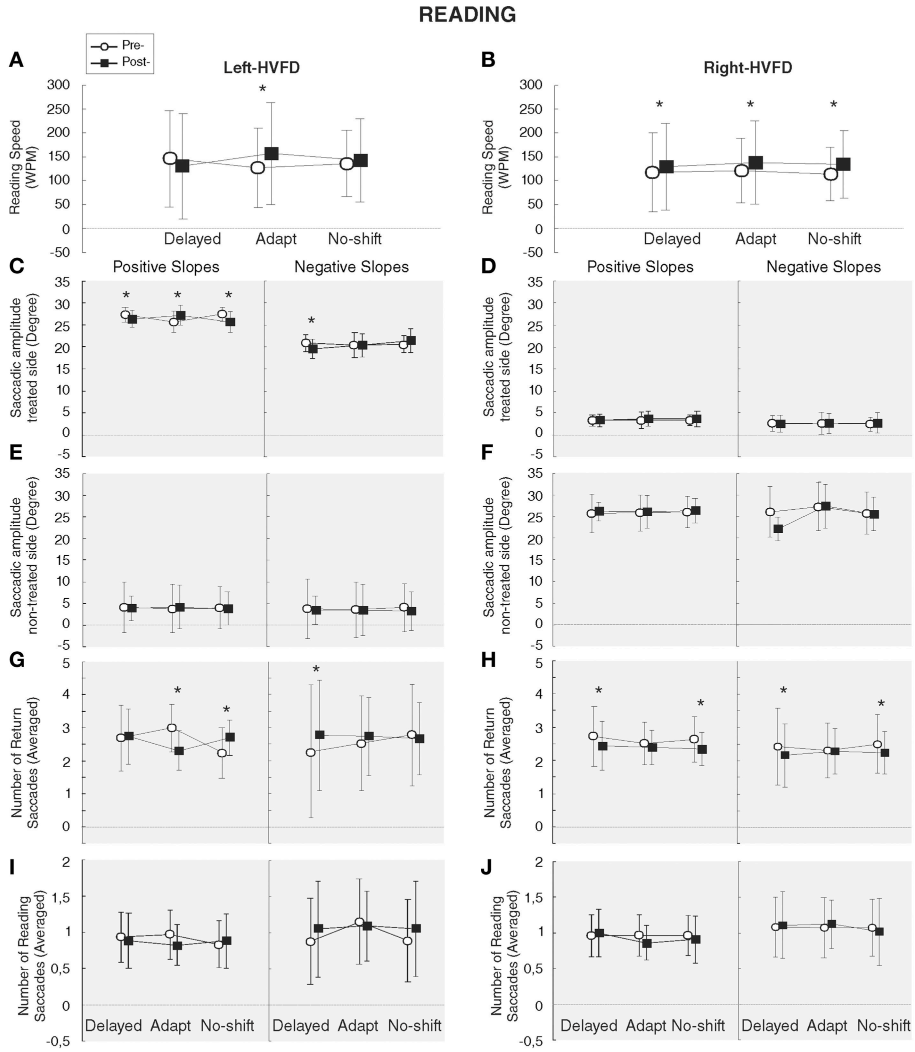


FIGURE 6 | Results of reading task. Functional and oculomotor (gray background) measures are represented separately for the left-HVFD **(A, C, E, G, I)** and right-HVFD **(B, D, F, H, J)** patients. Oculomotor measures include the amplitude of saccades toward the treated-side (**C,D**), non-treated side **(E,F)** in degree and the number of return (**G,H**) and reading (**I,J**) saccades. Bars represent the confident interval at 0.95. Stars represent the significant difference between pre- and post-phases revealed by *Post-hoc* LSD Fisher test.

In the next paragraphs we will discuss (1) the improvement of functional measures obtained following the AS training; (2) the improvement of oculomotor measures obtained specifically following the AS adaptation training; (3) finally, the usefulness of AS adaptation as a potential rehabilitation method and the different ways to increase its efficiency and long-term after-effects.

Functional Measures: Effects of Anti-saccade Training Paradigms?

Our results suggest that the 15 min of anti-saccade training is by itself sufficient to allow right-HVFD patients to read faster and all patients to explore faster. Indeed, after any of the three trainings, we observe a 4% improvement of reaction time in the Pop-out exploration task, a 7% improvement of reaction time in the Serial exploration task, and a 12% improvement of reading speed for the right-HVFD patients (**Table 4**). Due to absence of consensus about methods to evaluate the functional outcomes in the rehabilitation of HVFD (Bouwmeester et al., 2007), it is difficult to compare these findings to the literature. For example, several studies found a 46–48% improvement of visual exploration reaction time (according to Figure 5 of Zihl, 1995b), but testing only the blind side (Roth et al., 2009) or the best responsive subgroup (Pambakian et al., 2004; Keller and Lefin-Rank, 2010). Other studies revealed an improvement of reading performance ranging from 18 to 58% (Spitzyna et al., 2007) or from 53 to 96 WPM for right-HVFD patients (Zihl, 1995a; Keller and Lefin-Rank, 2010). However, as compared to ours, these studies were based on long training duration, on recruitment starting 3 months after the lesion and / or

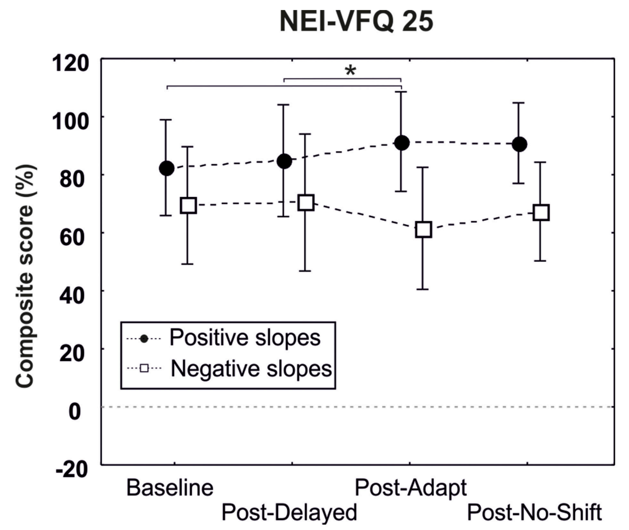


FIGURE 7 | Results of the questionnaire NEI-VFQ25. Composite score of patients with a macular spare superior to 5° are represented separately for patients having positive (black circles) and negative (white squares) slopes. Bars represent the confident interval at 0.95. Star represents the significant difference of the Baseline (pre-delayed-shift training) and the post-delayed training as compared to the post-adaptation training, as revealed by *Post-hoc* LSD Fisher test.

TABLE 4 | Percentage of modification ((post-phase – pre-phase)/ pre-phase)*100 (± SD) of functional measures for all tasks, separately for each training, and averaged over all the training (right column).

	Delayed-shift	Adaptation	No-shift	All training
POP-OUT				
Reaction time	10.48 (±12.57)	5.01 (±10.51)	–3.59 (±11.69)	3.97 (±12.76)
SERIAL				
Reaction time	8.93 (±7.67)	10.99 (±9.69)	1.92 (±13.09)	7.28 (±10.87)
READING				
Word per minute (all)	3.06 (±21.37)	17.68 (±14.12)	10.17 (±21.34)	10.30 (±19.68)
Word per minute Left-HVFD	–5.30 (±28.69)	24.20 (±12.98)	4.17 (±25.42)	7.69 (±25.10)
Word per minute Right-HVFD	8.29 (±15.22)	13.61 (±14.01)	13.92 (±19.22)	11.94 (±15.80)

Positive (negative) values represent an improvement (decline) of performance in post-phase relative to pre-phase.

on outcomes evaluation restricted to the material used during training. Still, our results are encouraging since they reveal significant effects, albeit smaller, for both visual exploration and reading following a very brief (15 min) training session.

Improvement of performance after a short-lasting saccadic training has already been observed in a controlled study (Jacquin-Courtois et al., 2013) using a 30 min training in a target ramp-step paradigm eliciting a sequence of pursuit and saccadic ocular movements toward the blind hemifield. Results disclosed a 23% improvement of the performance in an ecological version of Serial exploration task. In both their training paradigm and ours, a visuo-spatial cueing provided by the ramp target presented foveally and the static target presented in the healthy hemifield, respectively, provided the patient with information about the location of the target in the blind hemifield. Such cueing may crucially contribute to boost the performance and shorten the duration of the compensatory training in patients with HVFD. Note however that the cueing cannot explain the long-term and generalized benefit found in the present study, since in Jacquin-Courtois et al. (2013) the improvement shown for Serial-like exploration tasks did not generalize to Pop-out exploration and reading.

Previous studies have demonstrated that the training-related improvements in reading and visual exploration are highly specific and task-dependent (Schuett et al., 2009, 2012; Jacquin-Courtois et al., 2013). However, we demonstrate in the present study an effect of anti-saccade training on both reading (for right HVFD) and visual exploration tasks. Such generalization of saccadic training to different visual tasks has already been shown in a paradigm using an audio-visual training of 4 h daily over a period of 2 weeks in which the patient had to detect a visual stimulus in the blind hemifield, simultaneously presented with a temporally and spatially coincident sound (Passamonti et al., 2009; Keller and Lefin-Rank, 2010). In this audio-visual training, the authors suggested that the generalization was mainly due to low-level neural mechanisms (Bolognini et al., 2005): i.e., by using a multi-sensory integration paradigm their approach reinforces the activation of subcortical structures, specifically the Superior Colliculus, and of cortical areas which contribute to its multisensory activity (Passamonti et al., 2009).

Anti-saccades are not supposed to be based on low-level neural mechanisms but instead involve a large frontal network such as Frontal Eye Field (FEF), Supplemental Eye Field, and Dorsolateral Prefrontal Cortex (Everling and Munoz, 2000; Munoz and Everling, 2004; Pierrot-Deseilligny et al., 2004; McDowell et al., 2008). HVFD being due to either occipital or optic radiations lesions and the neural network involved in eye movements, including cortical areas described above for AS being usually spared (Nelles et al., 2007, 2009), we rather speculate than this extensive network might favor the generalization of AS training to other kind of saccades like those involved in reading and visual exploration in which FEF is also called for (Gitelman et al., 2002; Heinzle et al., 2010). We speculate that thanks to the use of this large network, this might have influenced and boosted high cognitive functions required for perceptual task.

Are Oculomotor Measures Changes Specifically Related to as Plasticity Mechanisms?

Despite a global improvement of functional measures in the visual tasks following all three trainings, the spatial (amplitude) or temporal (fixation) parameters of associated eye movements did not systematically change, in contrast to reports of previous controlled studies (Zihl, 1995a; Spitzyna et al., 2007; Passamonti et al., 2009). Zihl (1995a,b) has shown that repetitive sessions of saccadic training are necessary to improve eye movements in both reading and visual exploration tasks. In our study, the single training session might have been insufficient to trigger significant reorganization of eye movements. Furthermore, the observed dissociation between significant functional performance and absent oculomotor changes suggests that anti-saccade training might stimulate visuo-attentional functions. Changes in oculomotor measures were observed only following the adaptation training, a 15 min training which was sufficient to induce an amplitude increase of saccades in nine patients that could also be observed in the Serial exploration task and, for left-HVFD patients, in the reading task. These fast oculomotor changes suggest the involvement of the specific plasticity mechanisms elicited during saccadic adaptation, as discussed in the following.

First of all, we could not demonstrate a robust effect of the anti-saccade adaptation paradigm in the entire group of patients with HVFDs, as measured by the slopes of AS gain vs. trial number relationship during the training. However, a sub-group of nine patients showed a positive slope of the AS gain in the adaptation training, independently of their side of HVFD and their macular spare. In this sub-group, we could also demonstrate, and specifically following the adaptation training, an increase of saccade amplitude during the reading task (left-HVFD patients) and the Serial exploration task. Note however that patients of this sub-group did not show any change of saccades in the Pop-out task, as well as the right-HVFD patients in the reading task. We did not evaluate the laterality in our patients. However, the only difference between left and right-HVFD patients concerns the reading task, which we believe are related to reading direction rather than to hemispheric asymmetry or laterality. Furthermore, given the voluntary nature of anti-saccades, the stronger transfer of AS adaptation to saccades of the Serial exploration task than to saccades of the Pop-out exploration task is consistent with the fact that saccades in the Serial exploration task are triggered on a more voluntary basis than in the Pop-out exploration task.

In the reading task, right-HVFD patients did not present any oculomotor changes while left-HVFD patients did. Several arguments from the saccadic adaptation literature can explain this difference. First, according to the notion of adaptation field (Frens and van Opstal, 1994), adapting one single saccade transfers more to saccades of larger amplitude than to saccades with a shorter amplitude (Schnier et al., 2010). Since we adapted AS of 6° to 12°, this could explain the lack of transfer to rightward reading saccades of around 3–4° in amplitude for right-HVFD patients and the presence of transfer to leftward return saccades (around 25°) for left-HVFD patients. Another explanation is that the lack of after-effect on rightward saccades during the post-phase reading task results from a faster de-adaptation, due to the large number of saccades performed toward this direction as compared to leftward saccades (Alahyane and Pelisson, 2005). Finally, a last explanation would be that right-HVFD patients would need to train twice more than the left-HVFD to show oculomotor changes, as Zihl suggested in a previous study (Zihl, 1995a). We should however keep in mind that the effects are demonstrated on a small group of patients (left-HVFD patients), and that such effects should be further tested and reproduced in a larger group of patients.

Finally, the neural underpinnings of the functional benefits related to the involvement of specific plasticity mechanisms elicited during the AS adaptation training has still to be determined. Indeed, beyond the classical contribution of the cerebellum, the neural substrates of saccadic adaptation remains largely unknown, notably those of AS adaptation. Recent studies using fMRI (Blurton et al., 2012; Gerardin et al., 2012) or TMS (Panouilleres et al., 2014) in healthy subjects have revealed the involvement of parieto-frontal areas of the cerebral cortex in adaptation of reactive saccades and of scanning saccades, and studies in patients with a thalamic lesion provided evidence for a role of the cerebello-thalamo-cortical pathways for reactive saccades adaptation (Gaymard et al., 2001; Zimmermann et al., 2015). Concerning anti-saccades, our study demonstrating the possibility to induce AS adaptation in healthy subjects (Lévy-Bencheton et al., 2013) is to our knowledge the only study on AS plasticity so far. In this study, we speculated that the frontal cortex and its recurrent connections with the basal ganglia could be the locus of AS adaptation. According to this hypothesis, AS adaptation training in the present study could have changed the activity of these basal ganglia-frontal systems in HLH patients and led to functional improvements in tasks (reading, serial visual exploration) requiring not only accurate oculomotor control but also efficient "frontal functions" such as cognitive flexibility and short-term working memory.

Anti-Saccade Adaptation as a Potential Rehabilitation Method

The patients who showed an increase of the anti-saccade gain during the adaptation training (i.e., positive slope) also demonstrated some specific functional and oculomotor effects in the reading task. That specificity for the same subgroup of patients (i.e., positive slope) is also observed in the composite score of the quality of life questionnaire, which is significantly increased following the adaptation training for patients presenting a macular spare superior to 5°. This suggests that using outward adaptation of anti-saccades is a promising paradigm, whose effect might be further tested in more repetitive training.

The first advantage of such paradigm compared to previous ones is that saccadic adaptation is induced fast and effortless. The first study aiming at testing such an automatic strategy on reading performance showed that following a 15 h training (in right-HVFD only) patients presented a 18% increase of their reading speed (Spitzyna et al., 2007). In our study, for the sub-group of patients with a positive slope (i.e., "adapted-group") a significant improvement up to 24.20% was found in left-HVFD patients. This result is quite remarkable given the use of a single and short (only 15 min) session of eye movement training. For this reason, we think that adding an automatic component (adaptation) to the anti-saccade training improves the possibility to enhance performance.

Additionally, patients presenting a positive slope during the adaptation training seem to feel the benefice 1 month after the training as demonstrated by the specific increase of their composite score in this condition. Most importantly, the results reported that this efficiency occurs only for patients presenting a macular spare superior to 5° suggesting that they might have better facilities to detect the feedback target, (as compared to patients presenting a macular spare inferior to 5°), thus reinforcing the effect of plasticity mechanisms. However, it is important to underline that patients presenting a macular spare inferior to 5° do adapt as well, as suggested by their inclusion/presence in the subgroup of nine patients. Despite the small results, albeit promising, demonstrated in the post-phases during the computerized tasks (i.e., reading and visual explorations tasks) we should keep in mind that the patients explicitly reported an enhancement in their daily life activities and, this measure, although subjective, should be all the more taken into account in all studies focusing on rehabilitation methods.

Finally, even though our saccadic adaptation paradigm failed to induce functional effects on reading for right-HVFD patients, and in visual exploration tasks (although oculomotor changes occurred in the Serial exploration task), we suggest that a longer adaptation training would allow right-HVFD patients to reach the same level of performance than left-HVFD patients (Zihl, 2000). Repeating the 15 min protocol over 2 weeks could also help to increase the generalization of transfer to different visual tasks (Bolognini et al., 2005; Passamonti et al., 2009; Keller and Lefin-Rank, 2010) and its long term retention (Passamonti et al., 2009; Wang et al., 2012).

CONCLUSION

We demonstrate for the first time that 15 min of an anti-saccade adaptation training improves both reading and visual exploration tasks. Furthermore, all patients having a macular spare superior to 5° still benefit from the training at 1 month, as evaluated by a questionnaire on quality of life. Taken together, we believe that AS adaptation training, with some suggested improvements, could become an efficient and costless rehabilitation tool for patients suffering of HVFD.

AUTHOR CONTRIBUTIONS

DL, LP, DP, CT, and SJ contributed to the design of the experiments. RS designed saccadic program aiming at presenting computerized tasks on the screen. DL and MP performed experiments and conducted data analysis. DL, LP, DP, and CT interpreted the data. DL, LP, DP, CT, and SJ drafted, wrote, and approved the final version of the manuscript. CT supervised the project.

ACKNOWLEDGMENTS

This work was funded by PHRC 2010 (CT, principal investigator). This work was performed within the framework of the LABEX CORTEX (Grant ANR-11-LABX-0042) of University of Lyon, within the Investments in the Future Programme (Grant ANR-11-IDEX-0007) operated by the French National Research Agency.

REFERENCES

Alahyane, N., and Pélisson, D. (2005). Long-lasting modifications of saccadic eye movements following adaptation induced in the double-step target paradigm. *Learn. Mem.* 12, 433–443. doi: 10.1101/lm.96405

Blurton, S. P., Raabe, M., and Greenlee, M. W. (2012). Differential cortical activation during saccadic adaptation. *J. Neurophysiol.* 107, 1738–1747. doi: 10.1152/jn.00682.2011

Bolognini, N., Rasi, F., Coccia, M., and Làdavas, E. (2005). Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain J. Neurol.* 128, 2830–2842. doi: 10.1093/brain/awh656

Bouwmeester, L., Heutink, J., and Lucas, C. (2007). The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 78, 555–564. doi: 10.1136/jnnp.2006.103853

Everling, S., and Munoz, D. P. (2000). Neural correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *J. Neurosci.* 20, 387–400.

Frens, M. A., and van Opstal, A. J. (1994). Transfer of short-term adaptation in human saccadic eye movements. *Exp. Brain Res.* 100, 293–306. doi: 10.1007/BF00227199

Fujita, M., Amagai, A., Minakawa, F., and Aoki, M. (2002). Selective and delay adaptation of human saccades. *Brain Res. Cogn. Brain Res.* 13, 41–52. doi: 10.1016/S0926-6410(01)00088-X

Gaymard, B., Rivaud-Péchoux, S., Yelnik, J., Pidoux, B., and Ploner, C. J. (2001). Involvment of cerebellar thalamus in human saccade adaptation. *Eur. J. Neurosci.* 14, 554–560. doi: 10.1046/j.0953-816x.2001.01669.x

Gerardin, P., Miquee, A., Urquizar, C., and Pélisson, D. (2012). Functional activation of the cerebral cortex related to sensorimotor adaptation of reactive and voluntary saccades. *Neuroimage* 61, 1100–1112. doi: 10.1016/j.neuroimage.2012.03.037

Gitelman, D. R., Parrish, T. B., Friston, K. J., and Mesulam, M.-M. (2002). Functional anatomy of visual search: regional segregations within the frontal eye fields and effective connectivity of the superior colliculus. *Neuroimage* 15, 970–982. doi: 10.1006/nimg.2001.1006

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Res.* 18, 1279–1296. doi: 10.1016/0042-6989(78)90218-3

Halligan, P. W., Cockburn, J., and Wilson, B. A. (1991). The behavioural assessment of visual neglect. *Neuropsychol. Rehabil.* 1, 5–32. doi: 10.1080/09602019108401377

Harvey, M., and Milner, A. D. (1995). An investigation of hemispatial neglect using the landmark task. *Brain Cogn.* 27, 59–78. doi: 10.1006/brcg.1995.1004

Heinzle, J., Hepp, K., and Martin, K. A. C. (2010). A biologically realistic cortical model of eye movement control in reading. *Psychol. Rev.* 117, 808–830. doi: 10.1037/a0019575

Hier, D. B., Mondlock, J., and Caplan, L. R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology* 33, 345–350. doi: 10.1212/WNL.33.3.345

Hopp, J. J., and Fuchs, A. F. (2004). The characteristics and neuronal substrate of saccadic eye movement plasticity. *Prog. Neurobiol.* 72, 27–53. doi: 10.1016/j.pneurobio.2003.12.002

Jacquin-Courtois, S., Bays, P. M., Salemme, R., Leff, A. P., and Husain, M. (2013). Rapid compensation of visual search strategy in patients with chronic visual field defects. *Cortex J. Devoted Study Nerv. Syst. Behav.* 49, 994–1000. doi: 10.1016/j.cortex.2012.03.025

Keller, I., and Lefin-Rank, G. (2010). Improvement of visual search after audiovisual exploration training in hemianopic patients. *Neurorehabil. Neural Repair* 24, 666–673. doi: 10.1177/1545968310372774

Kerkhoff, G., Münßinger, U., Haaf, E., Eberle-Strauss, G., and Stögerer, E. (1992). Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. *Restor. Neurol. Neurosci.* 4, 245–254.

Kerkhoff, G., Münssinger, U., and Meier, E. K. (1994). Neurovisual rehabilitation in cerebral blindness. *Arch. Neurol.* 51, 474–481. doi: 10.1001/archneur.1994.00540170050016

Lévy-Bencheton, D., Pisella, L., Salemme, R., Tilikete, C., and Pélisson, D. (2013). Plastic modification of anti-saccades: adaptation of saccadic eye movements aimed at a virtual target. *J. Neurosci. Off. J. Soc. Neurosci.* 33, 13489–13497. doi: 10.1523/JNEUROSCI.0077-13.2013

Machner, B., Sprenger, A., Sander, T., Heide, W., Kimmig, H., Helmchen, C., et al. (2009). Visual search disorders in acute and chronic homonymous hemianopia. *Ann. N. Y. Acad. Sci.* 1164, 419–426. doi: 10.1111/j.1749-6632.2009.03769.x

McDowell, J. E., Dyckman, K. A., Austin, B., and Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain Cogn.* 68, 255–270. doi: 10.1016/j.bandc.2008.08.016

McLaughlin, S. (1967). Parametric adjustement in saccadic eye movement. *Percept. Psychophys.* 2, 359–362. doi: 10.3758/BF03210071

Morris, A. P., Kritikos, A., Berberovic, N., Pisella, L., Chambers, C. D., and Mattingley, J. B. (2004). Prism adaptation and spatial attention: a study of visual search in normals and patients with unilateral neglect. *Cortex* 40, 703–721. doi: 10.1016/S0010-9452(08)70166-7

Munoz, D. P., and Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nat. Rev. Neurosci.* 5, 218–228. doi: 10.1038/nrn1345

Nelles, G., de Greiff, A., Pscherer, A., Stude, P., Forsting, M., Hufnagel, A., et al. (2007). Saccade induced cortical activation in patients with post-stroke visual field defects. *J. Neurol.* 254, 1244–1252. doi: 10.1007/s00415-007-0511-1

Nelles, G., Pscherer, A., de Greiff, A., Forsting, M., Gerhard, H., Esser, J., et al. (2009). Eye-movement training-induced plasticity in patients with post-stroke hemianopia. *J. Neurol.* 256, 726–733. doi: 10.1007/s00415-009-5005-x

Pambakian, A. L. M., Mannan, S. K., Hodgson, T. L., and Kennard, C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. *J. Neurol. Neurosurg. Psychiatr.* 75, 1443–1448. doi: 10.1136/jnnp.2003.025957

Pambakian, A. L., Wooding, D. S., Patel, N., Morland, A. B., Kennard, C., and Mannan, S. K. (2000). Scanning the visual world: a study of patients with homonymous hemianopia. *J. Neurol. Neurosurg. Psychiatr.* 69, 751–759. doi: 10.1136/jnnp.69.6.751

Panouillères, M., Habchi, O., Gerardin, P., Salemme, R., Urquizar, C., Farne, A., et al. (2014). A role for the parietal cortex in sensorimotor adaptation of saccades. *Cereb. Cortex.* 24, 304–314. doi: 10.1093/cercor/bhs312

Passamonti, C., Bertini, C., and Làdavas, E. (2009). Audio-visual stimulation improves oculomotor patterns in patients with hemianopia. *Neuropsychologia* 47, 546–555. doi: 10.1016/j.neuropsychologia.2008.10.008

Pélisson, D., Alahyane, N., Panouillères, M., and Tilikete, C. (2010). Sensorimotor adaptation of saccadic eye movements. *Neurosci. Biobehav. Rev.* 34, 1103–1120. doi: 10.1016/j.neubiorev.2009.12.010

Pierrot-Deseilligny, C., Milea, D., and Müri, R. M. (2004). Eye movement control by the cerebral cortex. *Curr. Opin. Neurol.* 17, 17–25. doi: 10.1097/00019052-200402000-00005

Roth, T., Sokolov, A. N., Messias, A., Roth, P., Weller, M., and Trauzettel-Klosinski, S. (2009). Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study. *Neurology* 72, 324–331. doi: 10.1212/01.wnl.0000341276.65721.f2

Schnier, F., Zimmermann, E., and Lappe, M. (2010). Adaptation and mislocalization fields for saccadic outward adaptation in humans. *J. Eye Mov. Res.* 3, 1–18.

Schuett, S., Heywood, C. A., Kentridge, R. W., Dauner, R., and Zihl, J. (2012). Rehabilitation of reading and visual exploration in visual field disorders: transfer or specificity? *Brain* 135, 912–921. doi: 10.1093/brain/awr356

Schuett, S., Kentridge, R. W., Zihl, J., and Heywood, C. A. (2009). Are hemianopic reading and visual exploration impairments visually elicited? New insights from eye movements in simulated hemianopia. *Neuropsychologia* 47, 733–746. doi: 10.1016/j.neuropsychologia.2008.12.004

Spitzyna, G. A., Wise, R. J. S., McDonald, S. A., Plant, G. T., Kidd, D., Crewes, H., et al. (2007). Optokinetic therapy improves text reading in patients with hemianopic alexia A controlled trial. *Neurology* 68, 1922–1930. doi: 10.1212/01.wnl.0000264002.30134.2a

Trauzettel-Klosinski, S., and Brendler, K. (1998). Eye movements in reading with hemianopic field defects: the significance of clinical parameters. *Graefes Arch. Clin. Exp. Ophthalmol.* 236, 91–102. doi: 10.1007/s004170050048

Upton, N. J., Hodgson, T. L., Plant, G. T., Wise, R. J. S., and Leff, A. P. (2003). "Bottom-up" and "top-down" effects on reading saccades: a case study. *J. Neurol. Neurosurg. Psychiatr.* 74, 1423–1428. doi: 10.1136/jnnp.74.10.1423

Wang, J., Xia, R., Zhang, M., and Pan, Y. (2012). Long term retention of saccadic adaptation is induced by a dark environmental context. *Brain Res.* 1489, 56–65. doi: 10.1016/j.brainres.2012.10.018

Zangemeister, W. H., Oechsner, U., and Freksa, C. (1995). Short-term adaptation of eye movements in patients with visual hemifield defects indicates high level control of human scanpath. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* 72, 467–477. doi: 10.1097/00006324-199507000-00006

Zhang, X., Kedar, S., Lynn, M. J., Newman, N. J., and Biousse, V. (2006). Homonymous hemianopia in stroke. *J. Neuro-Ophthalmol.* 26, 180–183. doi: 10.1097/01.wno.0000235587.41040.39

Zihl, J. (1995a). Eye movement patterns in hemianopic dyslexia. *Brain* 118, 891–912.

Zihl, J. (1995b). Visual scanning behavior in patients with homonymous hemianopia. *Neuropsychologia* 33, 287–303.

Zihl, J. (2000). *Rehabilitation of Visual Disorders after Brain Injury*. Hove: Psychology Press.

Zimmermann, E., Ostendorf, F., Ploner, C. J., and Lappe, M. (2015). Impairment of saccade adaptation in a patient with a focal thalamic lesion. *J. Neurophysiol.* 113, 2351–2359. doi: 10.1152/jn.00744.2014

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 16 November 2015
doi: 10.3389/fnbeh.2015.00306

Evaluation of a Cognitive Rehabilitation Protocol in HIV Patients with Associated Neurocognitive Disorders: Efficacy and Stability Over Time

*Alessandro Livelli[1,2], Gian Carlo Orofino[1], Andrea Calcagno[3], Mariana Farenga[1], Donatella Penoncelli[1], Marta Guastavigna[1], Sinibaldo Carosella[1], Pietro Caramello[1] and Lorenzo Pia[2]**

[1] Division A of Infectious Diseases, Amedeo of Savoia Hospital, Torino, Italy, [2] SpAtial, Motor and Bodily Awareness Research Group, Department of Psychology, University of Torino, Torino, Italy, [3] Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

The primary aim of the present study was to evaluate the efficacy and stability over time of a cognitive rehabilitation protocol (restorative and compensatory approach) in HIV/AIDS patients with HIV-associated Neurocognitive Disorder (HAND). At baseline, 32 HIV/AIDS patients (16 with and 16 without HAND) were assessed with a neuropsychological battery (i.e., pre-assessment) consisting of 22 tests covering eight cognitive domains. Then, the experimental group was administered over 4 months a cognitive rehabilitation protocol aimed at improving four cognitive domains by means of eight paper and pencil/computer-based exercises. The control group received guideline-adherent clinical care (i.e., standard of care). At the end of the cognitive treatment, both groups were re-administered the neuropsychological battery (i.e., post-assessment). Additionally, 6 months after post-assessment, the experimental group was given the same neuropsychological battery (i.e., follow up-assessment). In order to test the efficacy of the cognitive rehabilitation protocol, we compared between groups the results of the neuropsychological battery at the pre- and post-assessments. In order to evaluate the stability over time, the effects of the cognitive rehabilitation protocol was examined comparing within the experimental group the results of the neuropsychological battery at post- and follow up-assessments. Our results show that the two groups did not differ at the pre-assessment, but differed at post-assessment. Specifically, the experimental group showed a significant improvement in five domains (Learning and memory, Abstraction/executive functioning, Verbal fluency, Attention/working memory, and Functional), whereas the control group significantly worsened in the same domains. The improvement of the experimental group did not change in the follow up-assessment in two domains (Abstraction/executive functioning, Attention/working memory, and Functional). Overall, these findings support the efficacy and, to some extent, the stability over time of our cognitive rehabilitation protocol.

Keywords: HIV, cognitive impairment, HIV-associated neurocognitive disorders, neurocognitive rehabilitation, HAND

OPEN ACCESS

Edited by:
Nuno Sousa, University of Minho, Portugal

Reviewed by:
Satoru Otani, Ryotokuji University, Japan
Jan Egil Nordvik, Sunnaas Rehabilitation Hospital, Norway

***Correspondence:**
Lorenzo Pia
lorenzo.pia@unito.it

***Received:** 25 April 2015*
***Accepted:** 30 October 2015*
***Published:** 16 November 2015*

Citation:
Livelli A, Orofino GC, Calcagno A, Farenga M, Penoncelli D, Guastavigna M, Carosella S, Caramello P and Pia L (2015) Evaluation of a Cognitive Rehabilitation Protocol in HIV Patients with Associated Neurocognitive Disorders: Efficacy and Stability Over Time. Front. Behav. Neurosci. 9:306. doi: 10.3389/fnbeh.2015.00306

INTRODUCTION

Combination antiretroviral therapy has extended the survival of patients living with Human Immunodeficiency Virus (HIV) and, as a result, HIV is becoming a chronic disease. At the same time, however, patients appear to be more commonly affected by physical, social and cognitive disabilities (e.g., O'Brien et al., 2014) than the general population. For instance, in a population-based sample of people living with HIV, over 80% of patients reported at least one impairment, activity limitation or social participation restriction (Rusch et al., 2004). One of the most common causes of disability is HIV-associated Neurocognitive Disorder (HAND; Heaton et al., 2010). The largest HAND study to date reported deficits in 52% of HIV-seropositive adults (Heaton et al., 2010). Since, these disabilities can affect clinical outcomes, cognitive rehabilitation may be a key step in the maintenance or improvement of quality of life of HIV patients.

Consensus research criteria for classifying HAND were published in 2007 (Antinori et al., 2007). Specifically, the authors proposed three categories: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD). The taxonomy is based on objective diagnostic criteria and account for daily functioning. The diagnosis of mild (MND) or severe (HAD) symptomatic HAND, for instance, requires a functional decline in at least two cognitive domains.

While the incidence of HAD has been reduced with combination antiretroviral therapy, the prevalence of less severe forms of neurocognitive disorders (i.e., ANI and MND) has remained relatively stable. Further, a large longitudinal study found that both ANI and MND were associated with cognitive worsening (Grant et al., 2014). One explanation for the persistence of mild HAND is antiretroviral neurotoxicity (Giunta et al., 2011; Robertson et al., 2012). Such toxicity may occur via direct drug effects on neurons and glia or indirectly via drug-linked effects on other organs, such as the cardiovascular system (Underwood et al., 2015).

The development of treatments for HAND is an important unmet clinical need. With regard to cognitive rehabilitation, three studies have been published to date (Boivin et al., 2010; Becker et al., 2012; Vance et al., 2012) but none employed HAND diagnoses as inclusion criteria and all used the so-called restorative approach that aims to restore the neural circuits underlying impaired cognitive processes by means of practice and focused training exercises. These studies reported positive effects on visual learning (Boivin et al., 2010) and speed of information processing (Boivin et al., 2010; Vance et al., 2012). However, the improvement did not extend to other ecologically relevant cognitive domains, such as executive functioning or working memory, and the durability of the benefits was not strongly addressed.

In the present study, we aimed to examine the efficacy and durability of a cognitive rehabilitation treatment for HAND in HIV+ adults taking suppressive antiretroviral therapy. To maximize the ecological impact of the training, our intervention combined the restorative approach of prior studies with the compensatory approach known to better enable learning of new strategies and minimizing the impact of remaining impairment (Robertson and Murre, 1999; Cicerone et al., 2005; Dams-O'Connor et al., 2009). We predicted a significant improvement of the neuropsychological picture in HAND-treated, respect to HAND-untreated patients. Additionally, we predicted the stability over time of these effects.

MATERIALS AND METHODS

Participants

Thirty-two patients (16 with and 16 without HAND) in care to the Infectious Disease Unit "Division A," Amedeo of Savoia Hospital (Turin, Italy) provided written informed consent to participate in the study, which was approved by the Local Bioethics Committee (ASL TO2). The study did not include any pharmacological intervention, and it was performed in accordance with the ethical standards described in the Declaration of Helsinki (World Medical Association, 2013).

Patients were randomized 1:1 to either the experimental group or the control group. The two groups did not differ in demographic, clinical, or treatment characteristics (all $p > 0.05$, see **Table 1**).

Both groups were administered a pre-assessment neuropsychological battery (see below). Then, the experimental group was given the cognitive rehabilitation intervention for 4 months (see below for the full description) and the control group was given standard of care. At the end of the cognitive treatment, both groups were re-administered (post-assessment) the neuropsychological battery. The experimental group was also given the neuropsychological battery 6 months after the post-assessment (follow up) in a within-subjects randomized order. Raw scores on each

TABLE 1 | Demographical/Clinical data of the two groups of patients and their statistical comparisons at baseline (pre-assessment).

	Experimental group	Control group	p
Sample size	16	16	>0.05
Plasma HIV-RNA[b] (≤ 50 c/mL)[2]	16	16	>0.05
Years HIV infected[a]	11.25 (5.8)	8.75 (6)	>0.05
Current CD4+ T-cell count[c]	539 (299–611)	614 (369–810)	>0.05
Nadir CD4 T-cell count[c]	212 (100–273)	177 (57–265)	>0.05
HCV seropositive[b] (%)	3 (19)	1 (6)	>0.05
Number of current antiretrovirals[c]	3 (3–4)	3 (3–4)	>0.05
CPE (CNS penetration effectiveness score) of current regimen[a]	7.1 (2)	7.5 (1.3)	>0.05
Age (years)[c]	47.5 (12.2)	50 (8.4)	>0.05
Ethnicity (Cau)[b]	16 (100)	14 (87.5)	>0.05
Education[c]	10 (3)	9 (3.9)	>0.05
Gender (Women)[b]	5 (31)	3 (19)	>0.05

Mean (SD) Median (IQR) or Number (%).
[a]*Mean (Standard deviation).*
[b]*Number (%).*
[c]*Median (Inter-quartile range).*

TABLE 2 | Groups' pre-, post-, and follow up- raw/T-scores on each test/domain of the neuropsychological battery.

Time	Domain/Test	Experimental group		Control group
		Raw scores	T scores	Raw scores
Pre-assessment	*Screening*		50.2 (5.3)	
	3Q	1.1 (1.1)	48.1 (11.1)	0.7 (0.9)
	MMSE	27.6 (1.27)	5.3 (8.3)	27.5 (1.4)
	IHDS	9.3 (1.7)	51.2 (10.5)	8.9 (1.6)
	Speed Information Processing		49.8 (7.9)	
	TMT-A	45.9 (20.5)	49.8 (10.1)	44.9 (20.6)
	STROOP-T	28.8 (11.4)	49.8 (11.1)	28.5 (9.4)
	Learning & Memory		51.1 (7.7)	
	RAVLT-IR	39.7 (9.3)	51.6 (9.4)	36.5 (10.1)
	RAVLT-DR	8.3 (2.8)	51.3 (8.9)	7.4 (3.5)
	ROCF-DR	10.4 (5.2)	50.3 (11.1)	10.1 (4.3)
	Abstraction/Executive Functioning		50.4 (5.4)	
	TOL	16.9 (1.5)	51.1 (10.2)	16.6 (1.5)
	STROOP-E	2.75 (1.8)	50.8 (7.5)	3.2 (3)
	TMT-B	149 (53.4)	52.9 (7.3)	190.7 (84.8)
	FAB	13.3 (3.3)	49.9 (12.4)	13.3 (1.98)
	ROCF-C	26.9 (5.5)	47.3 (10.6)	29.7 (4.6)
	Verbal Fluency		51.9 (8.2)	
	FAS	28.6 (9.3)	53 (10.8)	23.3 (7.3)
	VS	3.2 (0.6)	50.9 (10.5)	3.1 (0.5)
	Attention/Working Memory		50.6 (5.3)	
	CORSI	3.6 (0.8)	47.8 (9.98)	3.9 (0.75)
	DS	6.6 (1.9)	50.8 (9.6)	6.3 (2)
	TMT-BA	103.1 (41.2)	53.2 (6.4)	144.4 (77.4)
	Functional		49.6 (9.6)	
	IADL	7.2 (0.8)	49.6 (9.6)	7.2 (0.9)
	Mental Health		47.7 (10.3)	
	PHQ-9	10.4 (6.8)	47.9 (10.5)	7.6 (6)
	GAD-7	9.6 (6.2)	47.6 (10.9)	6.9 (4.9)
Post-assessment	*Screening*		53.3 (4.2)	
	MMSE	28.2 (0.8)	52.6 (6.6)	27.5 (1.6)
	IHDS	10 (0.7)	54 (4.6)	9.5 (1.8)
	Speed Information Processing		51.3 (8.1)	
	TMT-A	46.4 (15)	50.8 (9.5)	48.9 (16.9)
	STROOP-T	25.7 (10.9)	51.9 (9.97)	29.8 (10.9)
	Learning and Memory		55.7 (6.2)	
	RAVLT-IR	44.5 (8.1)	55.4 (7.9)	33.4 (9.3)
	RAVLT-DR	9.6 (3.5)	53.8 (9.8)	6.9 (3.2)
	ROCF-DR	20.5 (4.5)	58.1 (6.8)	9.7 (3.1)
	Abstraction/Executive Functioning		54.5 (2.8)	
	TOL	18 (0.9)	54.3 (5.9)	16.7 (1.7)
	STROOP-E	1.6 (1.4)	54 (5.1)	3.8 (3.3)
	TMT-B	128.6 (34.1)	52.2 (5.5)	155.9 (80.3)
	FAB	15.8 (1.1)	56.5 (5.3)	13.1 (1.9)
	ROCF-C	32.4 (1.7)	55.5 (5.2)	28.7 (3.6)
	Verbal Fluency		56.7 (4.3)	
	FAS	37.5 (7.3)	56.8 (6.9)	23 (8.3)
	VS	4 (0.5)	56.5 (6.8)	3.1 (0.6)

(Continued)

TABLE 2 | Continued

Time	Domain/Test	Experimental group		Control group
		Raw scores	T scores	Raw scores
	Attention/Working Memory		54.4 (4.9)	
	CORSI	4.7 (0.8)	53.4 (9.8)	4.1 (0.8)
	DS	9 (1.5)	56.4 (6.3)	6.1 (2)
	TMT-BA	82.2 (28.3)	53.4 (5.2)	119.1 (66.9)
	Functional		53.9 (5.6)	
	IADL	7.8 (0.4)	53.9 (5.6)	7.2 (0.9)
	Mental Health		49.5 (11.1)	
	PHQ-9	8.7 (6.3)	49.5 (10.9)	8.2 (5.4)
	GAD-7	6.8 (5.8)	49.6 (11.7)	6.4 (4.2)
Follow up-assessment	*Screening*		50 (5)	
	MMSE	28.8 (0.7)	50 (10)	
	IHDS	10.8 (0.9)	50 (10)	
	Speed Information Processing		50 (7.9)	
	TMT-A	38.2 (15.2)	50 (10)	
	STROOP-T	25.4 (8.5)	50 (10)	
	Learning and Memory		50 (7.9)	
	RAVLT-IR	49.8 (13.6)	50 (10)	
	RAVLT-DR	10.4 (2.6)	50 (10)	
	ROCF-DR	21.5 (5.1)	50 (10)	
	Abstraction/Executive Functioning		50 (3.6)	
	TOL	18.2 (0.7)	50 (10)	
	STROOP-E	1.9 (1.1)	50 (10)	
	TMT-B	114.4 (24.2)	50 (10)	
	FAB	16.1 (1)	50 (10)	
	ROCF-C	31.9 (2)	50 (10)	
	Verbal Fluency		50 (8.5)	
	FAS	38.2 (11.4)	50 (10)	
	VS	3.5 (0.6)	50 (10)	
	Attention/Working Memory		50 (6.9)	
	CORSI	4.7 (0.5)	50 (10)	
	DS	8.7 (1.2)	50 (10)	
	TMT-BA	73.8 (19.3)	50 (10)	
	Functional		50 (10)	
	IADL	7.9 (0.25)	50 (10)	
	Mental Health		50 (9.5)	
	PHQ-9	8.5 (4.8)	50 (10)	
	GAD-7	6.7 (3.6)	50 (10)	

Scores are corrected for age, educational level and gender in the Italian population.
3Q, Simioni's 3 question test, <1 pathological; MMSE, Mini Mental State Examination, <26 pathological; IHDS, International HIV Dementia Scale, <10 pathological; TMT-A, Trial Making Test Part A, >68 pathological; STROOP-T, Stroop Time, ≥31.66 pathological; RAVLT-IR, Rey Auditory Verbal Learning Test Immediate Recall, <32.26 pathological; RAVLT-DR, Rey Auditory Verbal Learning Test Delayed Recall, <5.8 pathological; ROCF-DR, Rey-Osterrieth Complex Figure Delayed Recall, ≤11.22 pathological; TOL, Tower of London, <15 pathological; STROOP-E, Stroop Errors, ≥2.81; TMT-B, Trial Making Test Part B, >177 pathological; FAB, Frontal Assessment Battery, <14.4 pathological; ROCF-C, Rey-Osterrieth Complex Figure Copy, ≤30.04 pathological; FAS, Phonemic Fluency; <21.33 pathological; VS, Verbal Span, <3.5 pathological; CORSI, Corsi block-tapping test, <3.76 pathological; DS, Digit Span, <8 pathological; TMT-BA, Trial Making Test Part BA, > 111 pathological; IADL, Instrumental Activity of Daily Living Questionnaire, ≤6 pathological; PHQ-9, Patient Health Questionnaire, >15 pathological; GAD-7, Generalized Anxiety Disorder, >15 pathological.
Mean (Standard error).

test are reported in **Table 2**. Scores were corrected for age, educational level and gender using Italian normative data. Since the Grooved Pegboard Test has no standardization, it is not reported.

Neuropsychological Battery

Initially, 220 consecutive HIV/AIDS patients were administered three different *screening tests* of the neuropsychological battery in a between-subjects randomized order:

- Mini Mental State Examination (MMSE; Folstein et al., 1975)
- International HIV Dementia Scale (IHDS; Sacktor et al., 2005)
- Simioni's 3 question test (3Q; Simioni et al., 2010)

Then, patients with a score below the cut off in MMSE, and/or at three questions test, and/or at the IHDS were administered in a between-subjects randomized order the rest of the neuropsychological battery ($N = 110$) composed by 19 tests covering seven different cognitive domains:

- *Speed of information processing*
  - Trail Making Test Part A (TMT-A, Giovagnoli et al., 1996)
  - Stroop Color Test-Time (STROOP-T, Caffarra et al., 2002a)
- *Learning and Memory*
  - Rey Auditory Verbal Learning Test Immediate Recall (RAVLT-IR, Carlesimo et al., 1996)
  - Rey Auditory Verbal Learning Test Delayed Recall (RAVLT-IR, Carlesimo et al., 1996)
  - Rey-Osterrieth Complex Figure Delayed Recall (ROCF-DR, Caffarra et al., 2002b)
- *Abstraction/Executive Functioning*
  - Tower of London simplified version (ToL; Allamanno et al., 1987)
  - Stroop Color Test-Errors (STROOP-E, Caffarra et al., 2002a)
  - Trail Making Test Part B (TMT-B, Giovagnoli et al., 1996)
  - Frontal Assessment Battery (FAB, Appollonio et al., 2005)
  - Rey-Osterrieth complex Figure Copy (ROCF-C, Caffarra et al., 2002b)
- *Verbal Fluency*
  - Phonemic Fluency (FAS, Carlesimo et al., 1995)
  - Verbal Span (VS, Spinnler and Tognoni, 1987)
- *Attention/Working Memory*
  - Corsi's block-tapping Test (CORSI, Orsini et al., 1987)
  - Digit Span (DS, Orsini and Laicardi, 1997)
  - Trail Making Test Part BA (TMT-BA, Giovagnoli et al., 1996)
- *Motor*
  - Grooved Pegboard Test Dominant and non- dominant hands (Heaton et al., 1991)
- *Functional*
  - Instrumental Activity of Daily Living Questionnaire (IADL, Lawton and Brody, 1969). This latter test was administered to investigate 10 areas of autonomy in activities of daily living: ability to use the phone, grocery shopping, preparing meals, take care of the house, laundry, moving away from home, assumption drugs, use of money, work ability, work efficiency.
- *Mental Health*
  - Patient Health Questionnaire (PHQ-9, Kroenke and Spitzer, 2002)
  - Generalized Anxiety Disorder (GAD-7, Kroenke and Spitzer, 2002)

Sixty of 110 tested patients (54%) were diagnosed with HAND (48 ANI, 10 MND, and 2 HAD). Participants ($N = 32$) were selected among those with HAND based on specific eligibility criteria: receiving antiretroviral therapy for at least 6 months, plasma HIV RNA below 50 copies/mL for at least 6 months, CD4+ T lymphocyte count above 350 cells/μ L from at least 6 months, fluent Italian speaker, and absence of severe comorbidities, including neurodegenerative or psychiatric disease, metabolic encephalopathy, psychoactive drug use, alcohol use, or head trauma.

Cognitive Rehabilitation Treatment

The cognitive rehabilitation protocol included both paper-and-pencil and computer-based exercises and it was composed of eight different exercises repeated in 36 sessions (around 50 min each) over 4 months. The eight tests were administered in a randomized-within subjects order. The protocol aimed at improving with the different group of tests four cognitive domains:

- *Attention*
  - Time Pressure Management (Fasotti et al., 2000)
    - Five minute paper-and-pencil exercise to improve functional impairments related to slowed information processing and complex attention. Patients learn compensatory strategies as, for instance, allowing sufficient time to manage a task
  - Attention Process Training Task (Cicerone et al., 2005)
    - Five minute paper-and-pencil exercise organized hierarchically to improve different components of attention: sustained, selective, alternating and divided attention. Patients learn compensatory strategies as, for instance, removing environmental distractors or employing using cues to maintain attention
- *Visual-verbal memory and learning*
  - COG.I.T.O. (open platform. ASPHI and San Camillo Hospital, Turin
    - Ten minute computer-based exercise to improve attention/visual-spatial memory. Patients have to encode daily-use objects in domestic environments (i.e., kitchen, bedroom, garage). Then, objects disappear and they have to put them back in their correct location, or recognizing them among distractors and relocating them, or writing their names and relocating them. From session to session, the available time decreases whereas the number of objects increases.

- Errorless Learning (Ehlhardt et al., 2005)
  - Five minute paper-and-pencil exercise providing sufficient cues during training so that patients can only give correct responses. Then, cues are progressively sequentially reduced
- Process-Oriented Memory Learning (Huildebrandt et al., 2006)
  - Five minute paper-and-pencil exercise to improve strategies adapted to different situations with memory requirements (e.g., practice, managing interferences between acquisition and recall, principles to optimize memory performance)

- *Executive Functioning and Working Memory*
  - Metacognitive Strategy Training (Kennedy et al., 2008)
    - Five minute paper-and-pencil exercise to improve daily problem-solving abilities (e.g., use of metacognitive approaches incorporating emotional self-regulation strategies which facilitates clear thinking)
  - Goal Management Training (Levine et al., 2000)
    - Five minute paper-and-pencil exercise to improve the ability to stop and think about what one is doing, identifying a specific goal, delineating the steps or achieve a goal and evaluating the outcomes
- *Metacognitive Awareness*
  - Increased Awareness (10 min)
    - One minute at the beginning of each session, 1 min at the end of each exercise for 10 min to improve awareness of neurocognitive deficits (Dams-O'Connor and Gordon, 2010).

RESULTS

Raw corrected scores on each neuropsychological test at pre pre-, post-, and follow up- were standardized (T-score). When necessary, the standard scores were reversed in order to keep the interpretation of all tests in the same direction, namely higher scores reflecting a better performance. Then the standard scores were averaged within each domain.

In order to evaluate the efficacy of the cognitive rehabilitation protocol, we performed a repeated measures ANOVA on each domain of the neuropsychological battery with the mean standard scores as dependent variables, TIME (two levels: pre-assessment, post-assessment) as within-subjects factor, and GROUP (two levels: experimental, control) as between-subjects factor.

Respect to "Screening," the TIME x group interaction resulted to be significant [$F_{(1, 30)} = 7.05$, $p = 0.013$]. *Post-hoc* comparisons (Duncan) revealed that the two groups did not differ at pre-assessment (experimental group: mean = 50.23, $SE = 1.32$; control group: mean = 49.77, $SE = 1.31$), but differed ($p = 0.007$) at post-assessment (experimental group: mean = 53.3, $SE = 1.74$; control group: mean = 46.7, $SE = 1.74$); see **Figure 1**. The analysis on "Speed information processing" was not significant. As regards "Learning and memory," the TIME × GROUP interaction was significant [$F_{(1, 30)} = 31.58$, $p < 0.0001$]. *Post-hoc* comparisons (Duncan) revealed that the two groups did not differ at pre-assessment (experimental group: mean = 51.11, $SE = 1.96$; control group: mean = 48.89, $SE = 1.95$), but differed ($p = 0.0002$) at post-assessment (experimental group: mean = 55.75, $SE = 1.54$; control group: mean = 44.24, $SE = 1.54$) because the mean score of the experimental group significantly ($p = 0.0005$) increased and the mean score of the control group significantly ($p = 0.0001$) decreased (see **Figure 1**). The TIME × GROUP interaction was significant [$F_{(1, 30)} = 21.42$, $p < 0.0001$ also for "Abstraction/Executive Functioning." Duncan *post-hoc* showed that the groups did not differ at pre-assessment (experimental group: mean = 50.41, $SE = 1.9$; control group: mean = 49.6, $SE = 1.38$), but differed ($p < 0.001$) at post-assessment (experimental group: mean = 54.51, $SE = 1.27$; control group: mean = 47.48, $SE = 1.27$) because the mean score of the experimental group significantly ($p = 0.003$) increased, and the mean score of the control group significantly ($p = 0.003$) decreased (see **Figure 1**). The same was true for the "verbal fluency" in which the TIME × GROUP interaction was significant [$F_{(1, 30)} = 11.45$, $p = 0.002$]. Duncan *post-hoc* analysis revealed that groups did not differ at pre-assessment (experimental group: mean = 51.95, $SE = 1.91$; control group: mean = 48.05, $SE = 1.91$), but

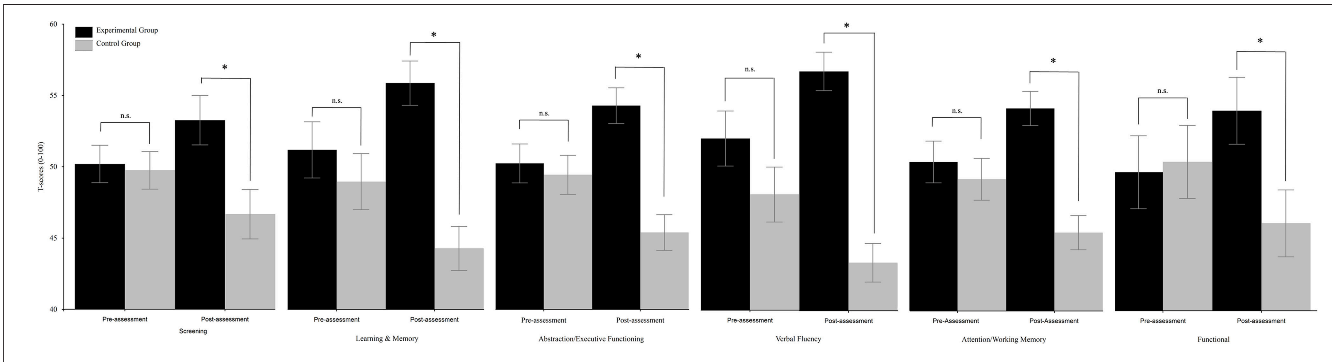


FIGURE 1 | Between-groups comparisons (domains) along time (pre- vs. post-assessment). Error bars represent standard errors. Asterisks indicate significant comparisons, n.s. indicate non-significant comparisons.

differed ($p < 0.0001$) at post-assessment (experimental group: mean = 56.66, SE = 1.34; control group: mean = 43.34, SE = 1.34) because the mean score of the experimental group significantly ($p = 0.02$) increased and the mean score of the control group significantly ($p = 0.02$) decreased (see **Figure 1**). The TIME × GROUP interaction was significant [$F_{(1, 30)} = 13.8$, $p = 0.001$] also for "Attention/Working memory." Duncan *post-hoc* analysis revealed that groups did not differ at pre-assessment (experimental group: mean = 50.62, SE = 1.49; control group: mean = 49.38, SE = 1.49), but differed ($p = 0.0001$) at post-assessment (experimental group: mean = 54.42, SE = 1.22; control group: mean = 45.58, SE = 1.22) because the mean score of the experimental group significantly ($p = 0.016$) increased and the mean score of the control group significantly ($p = 0.016$) decreased. The same was true for "Functional" in which the TIME × GROUP interaction was significant [$F_{(1, 30)} = 12.91$, $p = 0.001$]. Duncan *post-hoc* revealed that groups did not differ at pre-assessment (experimental group: mean = 49.64, SE = 2.54; control group: mean = 50.36, SE = 2.53), but differed ($p = 0.042$) at post-assessment (experimental group: mean = 53.92, SE = 2.31; control group: mean = 46.08, SE = 2.33) because the mean score of the experimental group significantly ($p = 0.021$) increased and the mean score of the control group significantly ($p = 0.021$) decreased. The analysis on "Mental Health" was not significant.

In order to evaluate whether the treatment was able to induce permanent effects, we performed in the experimental group a within subject ANOVA on each domain of the neuropsychological battery which improved from pre- to post assessments. The mean standard scores were employed as dependent variables, and TIME (three levels: pre-assessment, post-assessment, follow up-assessment) as within-subjects factor. The analysis on "Learning and Memory" (see **Figure 2**) resulted to be significant [$F_{(2, 30)} = 8.92$, $p < 0.001$]. *Post-hoc* comparisons (Duncan) revealed that the mean score significantly ($p = 0.003$) improved from pre- (mean = 51.1, SE = 1.94) to post- (mean = 55.75, SE = 1.55) assessment and worsened ($p < 0.001$) from post- to follow up-assessment (mean = 50, SE = 2.1). Also the analysis on "Abstraction/executive functioning" (see **Figure 2**) was significant [$F_{(2,30)} = 5$, $p = 0.008$] with the mean score significantly ($p = 0.006$) improved (Duncan) from pre- (mean = 50.4, SE = 1.44) to post- (mean = 54.52, SE = 0.7) assessment and worsened ($p = 0.004$) from post- to follow up-assessment (mean = 50, SE = 0.9). The same was true (see **Figure 2**) for "Verbal Fluency" [$F_{(2, 30)} = 5.5$, $p = 0.01$) with the mean score significantly ($p = 0.03$) improved (Duncan) from pre- (mean = 51.95, SE = 2.06) to post- (mean = 56.67, SE = 1.07) assessment and worsened ($p = 0.005$) from post- to follow up-assessment (mean = 50, SE = 2.1). As regards "Attention/working memory" (see **Figure 2**), the analysis resulted to be significant. However, *post-hoc* comparisons (Duncan) revealed that the mean score significantly ($p = 0.03$) improved from pre- (mean = 50.62, SE = 1.31) to post- (mean = 54.44, SE = 1.22) assessment but did not change ($p > 0.05$) from post- to follow up-assessment (mean = 50, SE = 1.74). The analysis on "Functional" (see **Figure 2**) was not significant ($p > 0.05$).

DISCUSSION

In the present study, we examined the efficacy of a cognitive rehabilitation protocol that included both restorative and

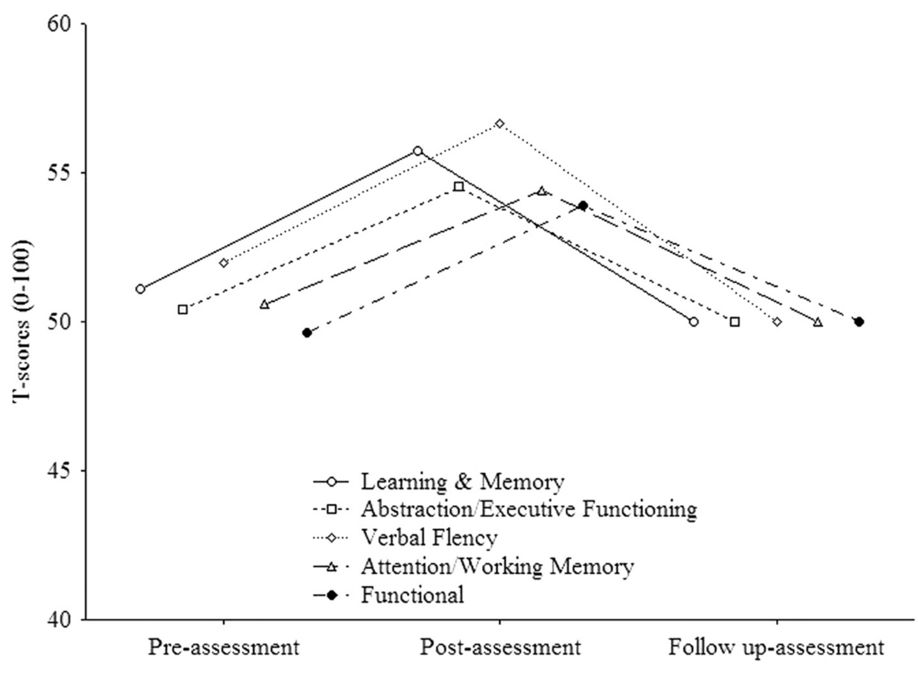


FIGURE 2 | Experimental group trends (improved domains) along time (post- vs. follow up-assessment.

compensatory approaches for treatment of HAND. Our results show discordant clinical evolution in five out of eight domains in participants who received the intervention compared with those who did not: treated patients improved, untreated patients worsened. Additionally, the improvement proved to be stable over time in four of five domains.

Within the context of HIV, rehabilitation is a dynamic set of activities that can benefit the disease as well as linked social limitations and dysfunctions (Worthington et al., 2005). With the graying of the HIV population, the demand for rehabilitation services will likely increase in the near future (O'Brien et al., 2014). Since a substantial number of HIV patients have cognitive impairment (e.g., Heaton et al., 2010), expansion in rehabilitation services should include cognitive rehabilitation.

One definition of cognitive rehabilitation is a systematic, functionally oriented set of therapeutic activities. Cognitive improvement is achieved by both strengthening previously learned behavioral patterns and establishing new, compensatory ones (Bergquist and Malec, 1997). This is possible because of the brain plasticity, the changes of brain organization that subserve short- and long-term behavioral modifiability. These changes can be structural (i.e., remodeling of the brain's physical structures) or physiological (i.e., dynamic adjustment of cellular processes such as synapse formation that modulate conductance or resistance to impulse transmission; see, for instance, Berlucchi, 2011). These changes can include adaptation to novel environments, maturation, different learning types, and compensatory changes in response to functional loss (see, for instance, Berlucchi, 2011).

Successful cognitive rehabilitation treatment typically targets different cognitive abilities, such as attention, memory, perception, learning, and executive functioning. Metacognitive awareness, emotional regulation, social skills and community integration are other, important targets. The main aim of cognitive rehabilitation is to significantly reduce the impact of disease on daily living. More specific aims depend on the nature and severity of the individual cognitive, behavioral, physical, and emotional difficulties as well as on the specific individual premorbid achievements (Dams-O'Connor and Gordon, 2010).

With HAND, HIV mainly affects fronto-striatal-thalamocortical circuitry, often being associated with decreased white matter volume (e.g., Thompson et al., 2005). As a consequence, cognitive deficits can cover a wide range of abilities. For instance, patients may develop impairments of visual/verbal working memory (Martin et al., 2001) as a consequence of central executive dysfunctions (Hinkin et al., 2002). Additionally, patients may show working memory impairments that can influence even higher-level cognitive abilities and daily activities (Martin et al., 2004). Nonetheless, HIV is frequently associated with difficulties of attentional processes (Hinkin et al., 2002), which, in turn, may negatively affect adherence to antiretroviral therapy (Levine et al., 2005, 2008). As a result, patients can experience multiple personal and professional difficulties and are frequently unemployed (Heaton et al., 1994; van Gorp et al., 2007).

In the present study, we aimed to maximize the effects of a cognitive rehabilitation intervention by training patients in both restorative (i.e., COG.I.T.O) and compensatory abilities (Time Pressure Management, Attention Process Training Task, Errorless Learning, Process-Oriented Memory Learning, Metacognitive Strategy Training, Goal Management Training, Increased Awareness). Each exercise was organized and administered in different steps with progressively increasing difficulty, suitable for gradual improvement of performance and for learning of any targeted ability. As written above, we found a significant improvement in the experimental, respect to the control, from pre- to post-assessments in Learning and memory, Abstraction/executive functioning, Verbal fluency, Attention/working memory, and Daily functioning. The improvement in Attention/working memory indirectly suggests benefits for daily functioning (working memory) and medication adherence (attention). The improvement in Learning and memory could explain the improvements in self-reported IADLs at post-assessment as well as the better work efficiency reported by treated patients. In contrast, the control group significantly worsened in the same domains.

At follow up-assessment, the cognitive improvement were stable (i.e., no significant difference respect to post-assessment) in two domains. It is worth noticing that previous long-term (i.e., 5 months to 1 year) benefits of cognitive rehabilitation (Tesar et al., 2005; Svendsen and Teasdale, 2006; Fink et al., 2010; Stuifbergen et al., 2012), have been related to patients continued use of learned strategies in ecological situations, as well as to the relevance of the intervention to the patient's daily functioning (Cicerone et al., 2000). Then, patients of experimental group used learned strategies in ecological contexts of daily living. However, in the other three domains, the experimental group's performance significantly worsened (and, indeed, this is also the overall trend). Broadly speaking, this is not surprising but, rather, consistent with the fact that most long-term follow up studies on the effects of acquired brain injuries show also some persisting effects (Klonoff et al., 1993; Dikmen et al., 2003; Wood and Rutterford, 2006). Additionally, ARV neurotoxicity and the potential HIV activities within the central nervous system acts against the cognitive rehabilitation process. Indeed, this might also explain, at least in part, the above-mentioned fact that the control group worsened from pre- to post-assessment.

Our study had several limitations. First, the sample size is relatively small. Hence, further studies with larger samples are required to validate the findings. Secondly, and more importantly, the control group was administered standard of care only but not a structured activity, raising the possibility that repeating *per se* the cognitive rehabilitation protocol might have a role in the improvement observed in the experimental group. This possibility is countered by the fact that benefit was not observed in all domains, which would have been seen if the improvement was solely due to practice. Still, this remains a limitation of our investigation and future studies should employ active control activities such as generalized compensatory cognitive training or low cognitive demand computer activities (Weber et al., 2013). Interestingly, those studies might address the effects of different kind of interventions: restorative approaches vs. compensatory interventions, purely computer-based vs. purely paper-based. Beyond the presence of a control condition, such strategies would better enable proof of concept for the use of cognitive rehabilitation in HAND.

In conclusion, our intervention was associated with better cognitive performance. According to a recent call to action (Weber et al., 2013), future studies should prioritize development of specific cognitive rehabilitation interventions for HAND, particularly with emphasis on two issues. First, while our center is similar to other Italian centers, a specific battery of standardized tests for HIV populations should be developed in Italy to generalize our findings to different countries. Secondly, the impact of cognitive rehabilitation on daily living, quality of life, and medication adherence has to be clarified. Since unawareness is in general a significant barrier to treatment (Ownsworth et al., 2002) and since more than 50% of people with HIV have poor insight of their cognitive deficits (Weber et al., 2013), more specific measures and more sensitive interventions should be developed.

ACKNOWLEDGMENTS

The study has been funded by G. Goria Foundation Scholarship "Master dei Talenti della Società Civile" to AL, a Gilead, Abbvie, MSD, BMS, Janssen-Cilag, ViiV Healthcare research grant to GO, a Gilead and Bristol Meyer-Squib research grant to AC, a ICONA research grant to MF and a ICONA research grant to MG. A special thanks to Amedeo of Savoia Hospital, Division A and the whole Department of Infectious Diseases. We are grateful to Scott Letendre who carefully checked the English.

REFERENCES

Allamanno, N., Della Sala, S., Laiacona, M., Pasetti, C., and Spinnler, H. (1987). Problem solving ability in aging and dementia: normative data on a non-verbal test. *Ital. J. Neurol. Sci.* 8, 111–119. doi: 10.1007/BF02337583

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 69, 1789–1799. doi: 10.1212/01.WNL.0000287431.88658.8b

Appollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., et al. (2005). The Frontal Assessment Battery (FAB): normative values in an Italian population sample. *Neurol. Sci.* 26, 108–116. doi: 10.1007/s10072-005-0443-4

Becker, J. T., Dew, M. A., Aizenstein, H. J., Lopez, O. L., Morrow, L., Saxton, J., et al. (2012). A pilot study of the effects of internet based cognitive stimulation on neuropsychological function in HIV disease. *Disabil. Rehabil.* 34, 1848–1852. doi: 10.3109/09638288.2012.667188

Bergquist, T. F., and Malec, J. F. (1997). Psychology: current practice and training issues in treatment of cognitive dysfunction. *Neurorehabilitation* 8, 49–56. doi: 10.1016/S1053-8135(96)00208-9

Berlucchi, G. (2011). Brain plasticity and cognitive neurorehabilitation. *Neuropsychol. Rehabil.* 21, 570–578. doi: 10.1080/09602011.2011.573255

Boivin, M. J., Busman, R. A., Parikh, S. M., Bangirana, P., Page, C. F., Opoka, R. O., et al. (2010). A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. *Neuropsychology* 24, 667–673. doi: 10.1037/a0019312

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., and Venneri, A. (2002a). Una versione abbreviata del test di Stroop: dati normativi nella popolazione italiana. *Rivista di Neurologia* 4, 111–115.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., and Venneri, A. (2002b). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol. Sci.* 22, 443–447. doi: 10.1007/s100720200003

Carlesimo, G. A., Caltagirone, C., and Gainotti, G. (1996). The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *Eur. Neurol.* 36, 378–384. doi: 10.1159/000117297

Carlesimo, G. A., Caltagirone, C., Gainotti, G., and Nocentini, U. (1995). Batteria per la valutazione del deterioramento mentale (parte 2): standardizzazione e affidabilità diagnostica nell'identificazione di pazienti affetti da sindrome demenziale. *Arch. Psicol. Neurol. Psichiatr.* 56, 471–488.

Cicerone, K. D., Dahlberg, C., Kalmar, K., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., et al. (2000). Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Arch. Phys. Med. Rehabil.* 81, 1596–1615. doi: 10.1053/apmr.2000.19240

Cicerone, K. D., Dahlberg, C., Malec, J. F., Langenbahn, D. M., Felicetti, T., Kneipp, S., et al. (2005). Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch. Phys. Med. Rehabil.* 86, 1681–1692. doi: 10.1016/j.apmr.2005.03.024

Dams-O'Connor, K., and Gordon, W. A. (2010). Role and impact of cognitive rehabilitation. *Psychiatr. Clin. North Am.* 33, 893–904. doi: 10.1016/j.psc.2010.08.002

Dams-O'Connor, K., Lebowitz, M., Cantor, J., Gordon, W., and Spina, L. (2009). Feasibility of a computerized cognitive skill-building program in an inpatient TBI rehabilitation setting. *Arch. Phys. Med. Rehabil.* 90, e19–e20.

Dikmen, S. S., Machamer, J. E., Powell, J. M., and Temkin, N. R. (2003). Outcome 3 to 5 years after moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 84, 1449–1457. doi: 10.1016/S0003-9993(03)00287-9

Ehlhardt, L. A., Sohlberg, M. M., Glang, A., and Albin, R. (2005). TEACH-M: a pilot study evaluating an instructional sequence for persons with impaired memory and executive functions. *Brain Inj.* 19, 569–583. doi: 10.1080/002699050400013550

Fasotti, L., Kovacs, F., Eling, P. A., and Brouwer, W. H. (2000). Time pressure management as a compensatory strategy training after closed head injury. *Neuropsychol. Rehabil.* 10, 47–65. doi: 10.1080/096020100389291

Fink, F., Rischkau, E., Butt, M., Klein, J., Eling, P., and Hildebrandt, H. (2010). Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial. *Mult. Scler.* 16, 1148–1151. doi: 10.1177/1352458510375440

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., and Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *Ital. J. Neurol. Sci.* 17, 305–309. doi: 10.1007/BF01997792

Giunta, B., Ehrhart, J., Obregon, D. F., Lam, L., Le, L., Jin, J., et al. (2011). Antiretroviral medications disrupt microglial phagocytosis of β-amyloid and increase its production by neurons: implications for HIV-associated neurocognitive disorders. *Brain* 4:23. doi: 10.1186/1756-6606-4-23

Grant, I., Franklin, D. R. Jr., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., et al. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology* 82, 2055–2062. doi: 10.1212/WNL.0000000000000492

Heaton, R. K., Clifford, D. B., Franklin, D. R. Jr., Woods, S. P., Ake, C., Vaida, F., et al. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology* 75, 2087–2096. doi: 10.1212/WNL.0b013e318200d727

Heaton, R. K., Grant, I., and Matthews, C. G. (1991). *Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications*. Odessa, FL: Psychological Assessment Resources, Inc.

Heaton, R. K., Velin, R. A., McCutchan, J. A., Gulevich, S. J., Atkinson, J. H., Wallace, M. R., et al. (1994). Neuropsychological impairment in human immunodeficiency virus-infection: implications for employment, HNRC

Group. HIV Neurobehavioral Research Center. *Psychosom. Med.* 56, 8–17. doi: 10.1097/00006842-199401000-00001

Hinkin, C. H., Hardy, D. J., and Mason, K. I. (2002). Verbal and spatial working memory performance among HIV-infected adults. *J. Int. Neuropsychol. Soc.* 8, 532–538. doi: 10.1017/S1355617702814278

Huildebrandt, H., Bussmann-Mork, B., and Schwendermann, G. (2006). Group therapy for memory impaired patients: a partial remediation is possible. *J. Neurol.* 253, 512–519. doi: 10.1007/s00415-006-0013-6

Kennedy, M. R., Coelho, C., Turkstra, L., Ylvisaker, M., Moore Sohlberg, M., Yorkston, K., et al. (2008). Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. *Neuropsychol. Rehabil.* 18, 257–299. doi: 10.1080/09602010701748644

Klonoff, H., Clark, C., and Klonoff, P. S. (1993). Long-term outcome of head injuries: a 23 year follow up study of children with head injuries. *J. Neurol. Neurosurg. Psychiatr.* 56, 410–415. doi: 10.1136/jnnp.56.4.410

Kroenke, K., and Spitzer, R. L. (2002). The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr. Ann.* 32, 509–521. doi: 10.3928/0048-5713-20020901-06

Lawton, M. P., and Brody, E. M. (1969). Assessment of older people: selfmaintaining and instrumental activities of daily living. *Gerontologist* 9, 179–186. doi: 10.1093/geront/9.3_Part_1.179

Levine, A. J., Hinkin, C. H., Castellon, S. A., Mason, K. I., Lam, M. N., Perkins, A., et al. (2005). Variations in patterns of highly active antiretroviral therapy (HAART) adherence. *AIDS Behav.* 9, 355–362. doi: 10.1007/s10461-005-9009-y

Levine, A. J., Hardy, D. J., Barclay, T. R., Reinhard, M. J., Cole, M. M., and Hinkin, C. H. (2008). Elements of attention in HIV-infected adults: evaluation of an existing model. *J. Clin. Exp. Neuropsychol.* 30, 53–62. doi: 10.1080/13803390601186684

Levine, B., Robertson, I. H., Clare, L., Carter, G., Hong, J., Wilson, B. A., et al. (2000). Rehabilitation of executive functioning: an experimental-clinical validation of goal management training. *J. Int. Neuropsychol. Soc.* 6, 299–312. doi: 10.1017/S1355617700633052

Martin, E. M., Pitrak, D. L., Weddington, W., Rains, N. A., Nunnally, G., Nixon, H., et al. (2004). Cognitive impulsivity and HIV serostatus in substance dependent males. *J. Int. Neuropsychol. Soc.* 10, 931–938. doi: 10.1017/S1355617704107054

Martin, E. M., Sullivan, T. S., Reed, R. A., Fletcher, T. A., Pitrak, D. L., Weddington, W., et al. (2001). Auditory working memory in HIV-1 infection. *J. Int. Neuropsychol. Soc.* 7, 20–26. doi: 10.1017/S1355617701711022

O'Brien, K. K., Ibáñez-Carrasco, F., Solomon, P., Harding, R., Cattaneo, J., Chegwidden, W., et al. (2014). Advancing research and practice in HIV andrehabilitation: a framework of research priorities in HIV, disability and rehabilitation. *BMC Infect. Dis.* 14:724. doi: 10.1186/s12879-014-0724-8

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., and Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital. J. Neurol. Sci.* 8, 539–548. doi: 10.1007/BF02333660

Orsini, A., and Laicardi, C. (1997). *WAIS-R Contributo Alla Taratura Italiana*. Firenze: Giunti OS.

Ownsworth, T. L., McFarland, K., and Young, R. M. (2002). The investigation of factors underlying deficits in self-awareness and self-regulation. *Brain Inj.* 16, 291–309. doi: 10.1080/02699050110103986

Robertson, I. H., and Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol. Bull.* 125, 544–575. doi: 10.1037/0033-2909.125.5.544

Robertson, K., Liner, J., and Meeker, R. B. (2012). Antiretroviral neurotoxicity. *J. Neurovirol.* 18, 388–399. doi: 10.1007/s13365-012-0120-3

Rusch, M., Nixon, S., Schilder, A., Braitstein, P., Chan, K., and Hogg, R. S. (2004). Impairments, activity limitations and participation restrictions: prevalence and associations among persons living with HIV/AIDS in British Columbia. *Health Qual. Life Outcomes* 2:46. doi: 10.1186/1477-7525-2-46

Sacktor, N. C., Wong, M., Nakasujja, N., Skolasky, R. L., Selnes, O. A., Musisi, S., et al. (2005). The international HIV dementia scale: a new rapid screening test for HIV dementia. *AIDS* 19, 1367–1374.

Simioni, S., Cavassini, M., Annoni, J. M., Rimbault Abraham, A., Bourquin, I., Schiffer, V., et al. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 24, 1243–1250. doi: 10.1097/QAD.0b013e3283354a7b

Spinnler, H., and Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 8(Suppl.), 1–120.

Stuifbergen, A. K., Becker, H., Perez, F., Morison, J., Kullberg, V., and Todd, A. (2012). A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis. *Clin. Rehabil.* 26, 882–893. doi: 10.1177/0269215511434997

Svendsen, H. A., and Teasdale, T. W. (2006). The influence of neuropsychologic rehabilitation on symptomatology and quality of life following brain injury: a controlled long-term follow-up. *Brain Inj.* 20, 1295–1306. doi: 10.1080/02699050601082123

Tesar, N., Bandion, K., and Baumhackl, U. (2005). Efficacy of a neuropsychological training programme for patients with multiple sclerosis - a randomised controlled trial. *Wien. Klin. Wochenschr.* 117, 747–754. doi: 10.1007/s00508-005-0470-4

Thompson, P. M., Dutton, R. A., Hayashi, K. M., Toga, A. W., Lopez, O. L., Aizenstein, H. J., et al. (2005). Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proc. Natl. Acad. Sci. U.S.A.* 102, 15647–15652. doi: 10.1073/pnas.0502548102

Underwood, J., Robertson, K. R., and Winston, A. (2015). Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS* 29, 253–261. doi: 10.1097/QAD.0000000000000538

Vance, D. E., Fazeli, P. L., Ross, L. A., Wadley, V. G., and Ball, K. K. (2012). Speed of processing training with middle-age and older adults with HIV: a pilot study. *J. Assoc. Nurses AIDS Care* 23, 500–510. doi: 10.1016/j.jana.2012.01.005

van Gorp, W. G., Rabkin, J. G., Ferrando, S. J., Mintz, J., Ryan, E., Borkowski, T., et al. (2007). Neuropsychiatric predictors of return to work in HIV/AIDS. *J. Int. Neuropsychol. Soc.* 13, 80–89. doi: 10.1017/S1355617707070117

Weber, E., Blackstone, K., and Woods, S. P. (2013). Cognitive neurorehabilitation of HIV-associated neurocognitive disorders: a qualitative review and call to action. *Neuropsychol. Rev.* 23, 81–98. doi: 10.1007/s11065-013-9225-6

Wood, R. L., and Rutterford, N. A. (2006). Psychosocial adjustment 17 years after severe brain injury. *J. Neurol. Neurosurg. Psychiatr.* 77, 71–73. doi: 10.1136/jnnp.2005.065540

World Medical Association (2013). Declaration of helsinki: ethical principles for medical research involving human subjects. *JAMA* 310, 2191–2194. doi: 10.1001/jama.2013.281053

Worthington, C., Myers, T., O'Brien, K., Nixon, S., and Cockerill, R. (2005). Rehabilitation in HIV/AIDS: development of an expanded conceptual framework. *AIDS Patient Care STDS* 19, 258–271. doi: 10.1089/apc.2005.19.258

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 23 February 2016
doi: 10.3389/fnbeh.2016.00028

Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial

Flavia Mattioli[1], Fabio Bellomi[1], Chiara Stampatori[1], Leandro Provinciali[2], Laura Compagnucci[2], Antonio Uccelli[3], Matteo Pardini[3], Giuseppe Santuccio[4], Giuditta Fregonese[4], Marianna Pattini[5], Beatrice Allegri[5], Raffaella Clerici[6], Annalisa Lattuada[6], Cristina Montomoli[7], Barbara Corso[8], Paolo Gallo[9], Alice Riccardi[9], Angelo Ghezzi[10], Marco Roscio[10], Maria Rosaria Tola[11], Chiara Calanca[11], Daria Baldini[12], Debora Trafficante[12] and Ruggero Capra[13]*

[1] Neuropsychology Unit, Spedali Civili of Brescia, Brescia, Italy, [2] Clinica Neurologica, University of Ancona, Ancona, Italy, [3] Clinica Neurologica, MS Center, University of Genova, Genova, Italy, [4] Neurology Unit, Azienda Ospedaliera Valtellina Valchiavenna, Sondrio, Italy, [5] Neurology Unit, Fidenza Hospital, Fidenza, Italy, [6] Neurology Unit, Como Hospital, Como, Italy, [7] Biostatistics Unit, Department of Public Health, Experimental and Forensic Medicine, Pavia University, Pavia, Italy, [8] National Research Council, Neuroscience Institute, Padova, Italy, [9] Clinica Neurologica, University of Padova, Padova, Italy, [10] UO Neurologia, MS Center, Gallarate Hospital, Gallarate, Italy, [11] UO Neurologia, Ferrara University, Ferrara, Italy, [12] UO Neurologia, Lecco Hospital, Lecco, Italy, [13] Multiple Sclerosis Center, Spedali Civili of Brescia, Brescia, Italy

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Giuliano C. Geminiani, Università Degli Studi di Torino, Italy
Steve Majerus, Université de Liège, Belgium

***Correspondence:**
Flavia Mattioli
flaviacaterina.mattioli@gmail.com

Received: *24 April 2015*
Accepted: *08 February 2016*
Published: *23 February 2016*

Citation:
Mattioli F, Bellomi F, Stampatori C, Provinciali L, Compagnucci L, Uccelli A, Pardini M, Santuccio G, Fregonese G, Pattini M, Allegri B, Clerici R, Lattuada A, Montomoli C, Corso B, Gallo P, Riccardi A, Ghezzi A, Roscio M, Tola MR, Calanca C, Baldini D, Trafficante D and Capra R (2016) Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial. Front. Behav. Neurosci. 10:28. doi: 10.3389/fnbeh.2016.00028

Cognitive rehabilitation in multiple sclerosis (MS) has been reported to induce neuropsychological improvements, but the persistence of these effects has been scarcely investigated over long follow ups. Here, the results of a multicenter randomized clinical trial are reported, in which the efficacy of 15 week domain specific cognitive training was evaluated at 2 years follow up in 41 patients. Included patients were randomly assigned either to domain specific cognitive rehabilitation, or to aspecific psychological intervention. Patients who still resulted to be cognitively impaired at 1 year follow up were resubmitted to the same treatment, whereas the recovered ones were not. Neuropsychological tests and functional scales were administered at 2 years follow up to all the patients. Results revealed that both at 1 and at 2 years follow up more patients in the aspecific group (18/19, 94% and 13/17, 76% respectively) than in the specific group (11/22, 50% and 5/15, 33% respectively) resulted to be cognitively impaired. Furthermore patients belonging to the specific group showed significantly less impaired tests compared with the aspecific group ones ($p = 0.02$) and a significant amelioration in the majority of the tests. On the contrary patients in the aspecific group did not change. The specific group subjects also perceived a subjective improvement in their cognitive performance, while the aspecific group patients did not. These results showed that short time domain specific cognitive rehabilitation is a useful treatment for patients with MS, shows very long lasting effects, compared to aspecific psychological interventions. Also subjective cognitive amelioration was found in patients submitted to domain specific treatment after 2 years.

Keywords: multiple sclerosis, cognitive rehabilitation, randomize clinical trial, neuropsychology

INTRODUCTION

Patients affected with multiple sclerosis (MS) often have a certain degree of cognitive impairment. Approximately 40–70% of patients present a certain degree of cognitive deficit, independently from disease duration, disease severity and physical disability (Chiaravalloti and DeLuca, 2008). This frequently contributes to the loss of employment, reduced social and working abilities and worsened quality of life (Pompeii et al., 2005; Putzki et al., 2009). The main affected cognitive areas are attention, information processing speed, memory and executive functions (Calabrese, 2006; Chiaravalloti and DeLuca, 2008; Duque et al., 2008; Prakash et al., 2008). The spontaneous evolution of cognitive deficits in MS is known to be worsening, as shown by a 10 years longitudinal study conducted on patients who were in large measure untreated, reporting the increase in the number of moderately or severely impaired MS patients and a reduction of mildly impaired ones over time. Among clinical predictors, incipient cognitive decline seems to be the major risk factor for further patents' deterioration in the short-term. In the long-term, the likelihood increases that also patients with initial cognitive preservation may deteriorate (Amato et al., 2006b).

Although cognitive deficits are prominent and detrimental in MS, surprisingly few studies investigated the effectiveness of cognitive training (Jønsson et al., 1993; Plohmann et al., 1998; Fink et al., 2010; Mattioli et al., 2010a; Amato et al., 2014; Chiaravalloti and DeLuca, 2015). Despite differences emerged between the results of early published studies—mainly depending on methodological issues, such as clinical heterogeneity across patients in terms of disability, type of cognitive impairment, type of MS and type of immunomodulatory drug they were prescribed (Thomas et al., 2006)—the most recent investigations provided convergent support to the usefulness of cognitive rehabilitation in MS (Rosti-Otajärvi and Hämäläinen, 2014). Particularly, episodic memory (Chiaravalloti et al., 2013), autobiographical memory (Ernst et al., 2015) and attention abilities (Mattioli et al., 2010a, 2012; Amato et al., 2014) and executive functions (Mattioli et al., 2010a) have been shown to significantly improve after a domain specific cognitive training in randomized clinical trials—either compared to no treatment or to a control treatment. The positive effects of these cognitive trainings have been reported both immediately after the end of the treatment (Mattioli et al., 2010b; Hubacher et al., 2015) and 6 months after the end (Mattioli et al., 2012; Chiaravalloti et al., 2013; Rosti-Otajärvi et al., 2013). An independent improvement also in depression—a frequently associated disorder in MS—and quality of life have also been shown after cognitive interventions (Mattioli et al., 2010a, 2012).

However, the above mentioned studies were all performed by one single center and only in one recent study (Mattioli et al., 2015) a multicenter approach has been used, providing supporting evidences of the reliability of the domain specific approach (Sprague et al., 2009). This study, the Sclerosi Multipla Intensive Cognitive Training (SMICT) is a multicenter randomized Italian clinical trial on relapsing remitting (RR) patients. It was aimed at comparing the efficacy of a domain specific cognitive training with a non specific psychological treatment over 2 years follow up. Preliminary data of this collaborative study with the results of the 1st year follow up, showed that patients treated with the domain specific approach had a significantly lower number of impaired cognitive tests and resulted to be cognitively recovered in a significantly higher proportion compared to those ones submitted to the non-specific psychological intervention (Mattioli et al., 2015). Furthermore, all the patients of the study were prescribed the same immunomodulatory drug, (in fact, different therapeutic regimens in previous trials could have been a confounding variable). Through the persistence at 1 year of the positive effects of domain specific cognitive interventions has been published, the exact need for treatment beyond the 1st year of follow up still needs to be further investigated and the possible beneficial effect of repeated boosters of cognitive training in MS patients still needs to be investigated as well.

The aim of the current article is to provide final results of the SMICT study over 2 years follow up in MS, evaluating the persistence over 2 years of cognitive improvement induced by the domain specific cognitive training. Also the possible efficacy of a repeated cognitive treatment in the 2nd year of follow up will be examined.

MATERIALS AND METHODS

Subjects

The Randomized Clinical Trial (Spedali Civili of Brescia trial Register NP: 560) was performed according to the Helsinki Declaration and after the approval of the Ethical Committee (Comitato Etico Provinciale di Brescia, January 2010). Patients' enrolment started on June 2010 and ended 31 December 2011. It involved 10 MS centers in Italy. Patients affected with MS, according to Poser and Brinar (2001) criteria with a RR course were included in the study, after their signed informed consent was obtained. To participate in the study, all patients needed to have been prescribed interferon beta 1A 44 mcg 3 times/week no later than 6 months before, in order to have the same drug regimen in patients. This first line therapeutic regimen was chosen, as it has been shown to be effective on several neuropsychological measures (Amato et al., 2013). Patients were included only if impaired (age corrected z score < -1.5 SD to norms) in at least one of the tests included in the Italian version of the Rao Brief Repeatable Battery and Stroop test. Exclusion criteria were dementia (excluded by means of anamnestic reports as well as MMSE >24 in patients), previous or present psychiatric disorders (requiring pharmacological treatment) and clinically evident relapse in the previous 6 months. For the included patients, the disease duration, the disability in the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), the relapse rate and steroid consumption (grams of intra venous methylprednisolone) in the previous year were registered.

Neuropsychological Evaluations

Three neuropsychological evaluations were performed for each patient: T0 at baseline before enrolment, T12 after 1 year and T24 after 2 years from the baseline. The Italian version of the Rao's Brief Repeatable Battery (Amato et al., 2006a), including Paced Auditory Serial Addition Task (PASAT 2″, PASAT 3″), Simbol Digit Modality Test (SDMT), Spatial Recall Test (SPART) 10/36 and Delayed Recall (SPART D), Selective Reminding Test Long Term storage (SRT LTS), Consistent Long Term Retrieval (SRT CLTR), Delayed Recall (SRT DR), the Controlled Oral Words Association (COWA) with the Phoneme (P) and Category (C) modalities (Mattioli et al., 2010a) and Stroop test (Barbarotto et al., 1998). Alternative forms, when available, were used, in order to avoid test retest effects and learning effects (Goretti et al., 2014). All the tests were corrected by age and education, according to published norms. A test was considered impaired, if its corrected score fell below −1.5 SD.

In addition, three functional scales were administered, in order to evaluate the fatigue (Modified Fatigue Impact Scale, mFIS; Kos et al., 2006), the possible deflection of mood (Montgomery-Asberg Depression Rating Scale, MADRS; Montgomery and Asberg, 1979) and the quality of life (Multiple Sclerosis Quality of Life Questionnaire, MSQoL; Solari et al., 1999) at the same intervals.

In order to measure the patients' subjective perception of cognitive amelioration after treatment, the item 6 of MADRS has been selected and used: it requires the patient to rate on a 6 point Likert scale his/her difficulties in collecting one's thoughts, where 0 means "no difficulty in concentrating" and 6 means "unable to read or converse without great difficulty" and compared between T0 and T24.

Treatments

Patients were randomly assigned to Specific Treatment Group (SG) or to Aspecific Treatment Group (AG), for 15 consecutive weeks with 2 weekly 60' sessions. Randomization (according to a computer-generated list of random number) and statistical analysis of data were carried out by an independent center, from whom all the Centers received the patients' number.

Specific Treatment

Specific treatment was administered according to the impaired neuropsychological function: Plan a Day software of the Rehacom[1] was used if a patient resulted impaired in executive functions (that is if his/her poor score was in the Stroop test or in the COWA P or COWA/C); Memory software of the same package was used if the patient was impaired in either the SRT or SPART verbal or spatial memory measures and the previously described 29 A/IP training, if he/she resulted impaired in attention/speeded information processing domain (pathological PASAT 2″, PASAT 3″, SDMT). If a patient was impaired in more than one domain, all the single domain trainings were balanced in the hourly session each time. Exercises complexity was adapted each time to the severity of each single patient's impairment in the selected domain, with the aim that the exercise had to be challenging in each treatment session.

[1] www.schuhfried.at

Plan a Day

The Plan a Day procedure trains the patient's ability to organize, plan and develop solution strategies, employing realistic simulations of a set of scheduled dates and duties to be organized at specific places in a virtual small city map. Times for planning and schedules are registered for each patient at each session and only improvement and acquisition of sufficient planning abilities for fulfilling all the appointments required led to an improved level in the following treatment session. Fifty four levels of increasing complexity are available, in order to challenge any grade of impairment. This was considered a strategic behavior acquisition. For further description of the treatment see Mattioli et al. (2015).

Memory

Patients were asked to give answer to multiple choice or open questions about tales of increasing length, which were presented on the PC, whose complexity was chosen on the basis of the patient's memory impairment. Ten levels of difficulty—also with interfering condition of two or three tales alternatively presented with the other tales' questions—were progressively presented to the patients.

A/IP Training

A specific speeded information training with increasing velocity (from 4000 to 1800 ms interval), which has been shown to be effective in patients with brain injuries, was used, consisting of a modified PASAT task with numbers, words and months of the year, according to Serino et al. (2006) procedure.

Aspecific Training

The A treatment (not domain specific intervention, but a generic psychological intervention, considered as control treatment) was conducted by the psychologist addressing the following items with the patient: the patient's disease perception (with the aid of scientific articles dealing with MS), eventual limitation in the patient's occupation due to MS, possible difficulties on his/her job, problems with the patient's family life and leisure activities, specific problems of the patient's due to MS (i.e., sexual, affective). The aim of this sort of psycho education was not to specifically treat a cognitive ability, but rather to discuss with the patient about the functional impairment due to MS, avoiding to treat depression or to have any behavioral or psychoanalytic approach. This type of psycho educational treatment, considered as a control treatment have been accepted as ethical by the Ethical Committees of all the Centers, as no sure evidences exist till now about the superiority of domain specific treatments of memory, attention and executive functions on the aspecific psychological approaches in MS.

All the treating psychologists were trained by attending 10 consecutive training meetings with the psychologists of the coordinator center.

The same treatment administered after randomization was repeated in the 2nd year of the study, after T12 evaluation, only if a patient resulted to be still impaired in at least one neurpsychological test.

Patients' neuropsychological evaluations and treatments were done by different neuropsychologists and performed in a quiet room, according with standardized published procedures, with maximum attention paid by the neuropsychologists in order to avoid interference from possible low motivation of patients on performance. All the patients were reminded about the study protocol in each session, in order to refresh the context of the evaluations.

Statistical Analysis

A sample size of 14 patients for each group was necessary (Faul et al., 2007) in order to have a 5% significance level and a 90% statistical power. Descriptive statistics are expressed as median and/or means ± SD. Due to the nature of the variables and the sample size, non-parametric tests were performed. The two patients'groups were compared using Mann-Whitney's statistic test for quantitative variables and Fisher's exact test for qualitative variables.

Pearson chi-squared test was applied to qualitative data. Repeated measures within group were evaluated by Wilcoxon signed-rank test (over two-time point) and by Friedman's test (over the three-time point). Repeated measures mixed models were applied to each variable to take into consideration simultaneously the effect of treatment, time and their interaction. All statistical analyses were performed using STATA/SE version 12.1 software and a $p < 0.05$ was considered significant. A Poisson multivariate regression model has been used to analyze the relationship between number of pathological tests and treatment, using EDSS as a covariate.

RESULTS

The AG consisted of 19 patients both at T0 and at T12. Eighteen of them resulted to be still impaired at T12 (that is they had at least one impaired test in the neuropsychological battery), two of which refused to repeat the neuropsychological evaluation at T24, so 16 patients in the AG repeated the aspecific treatment. In the SG, which at T0 and T12 consisted of 22 subjects, of whom 11 were still impaired at T12, 8 subjects refused to repeat the neuropsychological evaluation and only three patients repeated the treatment (with the same domain specific intervention as in the 1st year). **Figure 1** reports the CONSORT diagram. Comparing the number of patients who were still cognitively impaired at T12 between groups, a significantly higher number in the AG than in SG was found (16/17, 94% vs. 3/15, 20%, Pearson test $p = 0.014$). Also at T24 a significantly higher number (13/17) of patients in the AG than in the SG (5/15) resulted to be still cognitively impaired (Pearson test $p = 0.014$). This sample was considered for statistical analysis of single tests' scores.

As previously reported (Mattioli et al., 2015) baseline (T0) clinical characteristics of patients did not differ between groups in terms of disease duration, age, education, EDSS, steroid consumption and number of relapses. At T12 only EDSS score was changed between groups, which resulted to be higher in patients submitted to the Aspecific Treatment compared with patients submitted to the Specific Treatment (**Table 1**). Within group change revealed a worsened EDSS in AG at T24 (mean EDSS 3.47, SD 1.76; repeated measures mixed models: significant effect of both group and time, as well as interactions: $p = 0.003$, $p = 0.019$, $p = 0.002$) and an unchanged EDSS in SG. However, the number of relapses was not significantly different between the two groups at T24 (Mann Whitney $p = 0.99$), with a decrease compared with the number in the previous year in both groups. Similarly, steroid consumption decreased in the 2nd year follow up, not significantly different between groups (Mann Whitney test $p = 0.3$), indicating an overall similarity between disease physical severity between the groups.

As shown in **Table 2** the number of impaired tests in AG was not significantly changed between T0 and T24 ($p = 0.51$), while in the SG a significant reduction of impaired tests was observed ($p < 0.001$). Considering the comparison between AG and SG also at T12 in the number of impaired tests a significant reduction of them was found in the SG (**Table 2**). In addition, a between group comparisons of the number of pathological tests at T24 further confirms less impaired tests in SG compared with the AG (0.75 ± 1.34, 2.29 ± 2.52, $p = 0.02$). However, in a multivariate analysis, taking into account EDSS as a covariate, the difference in the number of pathological tests between AG and SG group loses its statistical significance ($p = 0.089$).

On the other hand, no differences emerged in MSQoL, mFIS and MADRS between groups at T24 (**Table 3**).

Also single tests' performance at T24 revealed significantly better performances of SG group compared to AG in SDMT (35 vs. 46, $p = 0.02$) and COWAL (30 vs. 35, $p = 0.006$), with a trend toward significance in SPART DR (five vs. seven, $p = 0.055$). Subjects in SG significantly improved their scores in almost all neuropsychological tests after both 1 and 2 years (**Table 4**), whereas subjects in AG did not significantly improved their scores in none of the tests. In repeated measures mixed models, interactions between treatment and time was statistically significant for PASAT 3″, SPART DR, SDMT and Stroop test and marginally significant for SPART 10/36 ($p = 0.0649$) and SRT LTS ($p = 0.0556$). These results confirm the significant difference on the neuropsychological tests between the two groups at the different follow ups, showing differences at T12 and at T24. Noteworthy, considering only the three patients of the SG, who, as being impaired at T12, were submitted to repeated rehabilitation the second time, they resulted to be unchanged at T24, in terms of number of impaired tests. The patients were all impaired in memory (of them one also impaired in attention and another in executive function), but, due to the small number, no statistical analysis on the effects of the training between domains was carried on.

Although the total MADRS score did not differ between groups, the results on MADRS item 6 measuring the subjective perception of cognitive deficits, resulted to be significantly reduced in SG (median T0 2, median T24 0; $p = 0.0182$ Wilcoxon signed rank test) and unchanged in the AG (median T0 2, median T24 2; $p = 0.88$ Wilcoxon signed rank test) and to be significantly better in SG than in the AG at T24 ($p = 0.291$ Mann Whitney test), showing a better subjective perception of cognitive performance in SG.

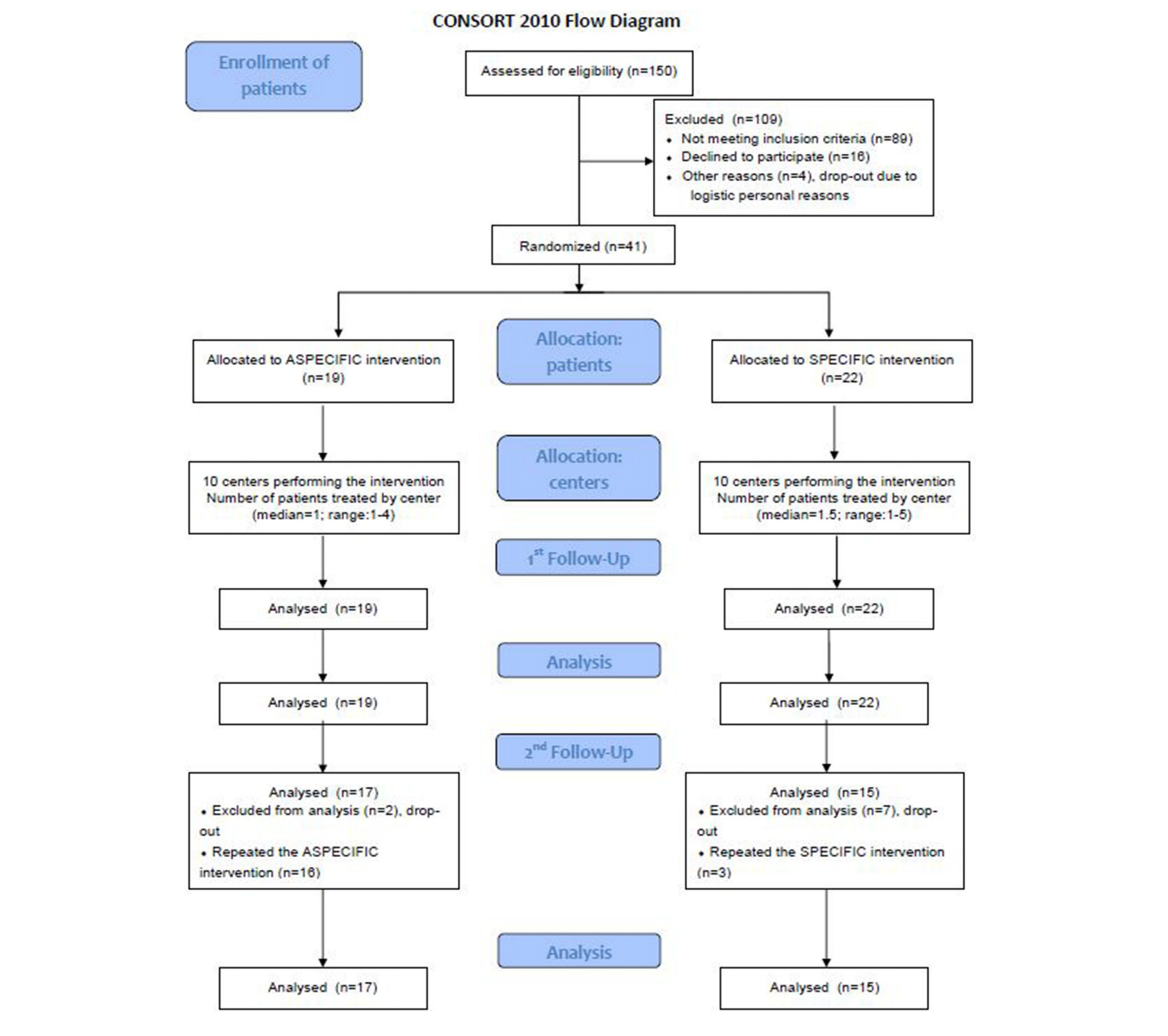


FIGURE 1 | Consort diagram of the study.

TABLE 1 | Characteristics of patients at T12.

	AG (n = 17)		SG (n = 15)		p-value*
	Median	Mean ± SD	Median	Mean ± SD	
Age (years)	49	44.88 ± 9.96	47	44.80 ± 8.69	0.75
Years of education	13	12.12 ± 3.62	10	10.93 ± 3.17	0.41
Disease duration (months)	60	87.18 ± 74.83	30	67.20 ± 88.77	0.10
Number of relapses (previous year)	0	0.53 ± 0.94	0	0.33 ± 0.62	0.72
EDSS	3	2.97 ± 1.49	2	1.63 ± 0.95	0.0094
Steroid (gr)#	0	2.29 ± 4.40	0	0.71 ± 1.82	0.30

**Mann-Whitney test. AG, Aspecific Treatment Group; SG, Specific Treatment Group; EDSS, Expanded Disability Status Scale. #Methylprednisolone consumption in the 1st year of the study.*

TABLE 2 | Number of pathological tests at baseline (T0) and after rehabilitation (T24), and between groups comparison (*) at T24.

	AG (*n* = 17)				SG (*n* = 15)				
	T0 *m*	T12^ *m*	T24 *m*	*p*-value**	T0 *m*	T12 *m*	T24 *m*	*p*-value**	*p*-value*
Number of pathological tests	2	3	2	0.5169	2	0	0	*0.0006*	*0.0162*

**Wilcoxon signed-rank test. *Mann-Whitney test at T24. ^Wilcoxon signed rank test: AG T0 vs. T24 p = 0.51; SG T0 vs. T24 p = 0.006.*

DISCUSSION

The main result of the present study is that domain specific cognitive rehabilitation can be effective and can sustain significant cognitive improvements up to 2 years in patients with RR MS. Specific exercises aimed at treating the impaired cognitive domain are shown to induce significantly better results both on cognition and on subjective perception of cognitive impairment in patients, compared with non domain specific psychological interventions. Results showed the greater amelioration both considering the reduction in the number of impaired neuropsychological tests and the improvement in single tests' scores over time. Particularly, nearly all (94%) patients assigned to aspecific treatment and only 20% of those assigned to the specific treatment, needed the repeated rehabilitation in the 2nd year of follow up. This indicates that the domain specific intervention provided in the 1st year caused beneficial effects lasting up to 2 years. Notably, the only three patients, who—being still impaired at T12—needed a repeated treatment, did not change in severity their cognitive impairment, measured as the number of impaired tests. The uselessness of repeated treatments in neuropsychological rehabilitation of MS is in line—although with longer time of follow up—with the conclusions of Chiaravalloti et al. (2013), who found no effects of repeated booster sessions of memory rehabilitation in their study.

Moreover, after 2 years, patients assigned to the SG showed fewer impaired neuropsychological tests compared to those assigned to AG and also had a significantly better performance in tests measuring information processing speed and executive functions. Finally SG patients perceived a subjective improvement in their cognitive performance, whereas AG patients did not. This finding is relevant in MS, as shows that appropriately conducted cognitive rehabilitation can be able to reduce the worsening spontaneous evolution of cognitive impairment of MS patients and beneficially impact on their disease relate disability over time.

TABLE 3 | T24 MSQoL, mFIS and MADRS scores in AG and SG.

	AG (*n* = 17) median	SG (*n* = 15) median	*p*-value*
MSQoL	140	161	0.14
mFIS	32	20	0.27
MADRS	5	5	0.34
EDSS	3	1.5	0.005

**Mann-Whitney test at T24.*

The cognitive improvement found in SG is, in our opinion, only ascribed to the type of the treatment assigned, as the other clinical variables were not different between groups, as well as the type of the pharmacological treatment used and the disease severity. Although, it is worth noting that a possibly higher disease activity in AG compared to SG cannot be totally ruled out: throughout the study, EDSS—relatively low in both groups—worsened in AG and remained substantially stable in SG. On the other hand steroid consumption and relapse rates were not different between groups across 2 years follo up. Furthermore, it is known that EDSS relies more on physical than on cognitive disability; so it is possible that, at individual level, physical disability worsened more in AG patients due to less response to immunomodulatory drug instead of more active disease. Furthermore, a different response to interferon can be hypothesized in AG compared to SG and also possible spinal or cerebellar new lesions (that would not be relevant under a cognitive point of view) could have also been responsible for motor/EDSS worsening). Overall, it is reasonable to conclude that—although neuroradiological data on new lesions are missing in this study-, disease activity relevant for cognitive worsening can reasonably be considered similar between groups; not the same for motor disability.

The possibility of successfully rehabilitate MS patients' cognitive impairment with domain specific PC assisted, replicable and easily to administer rehabilitative programs in the clinical setting, with long standing results up to 2 years, has never been demonstrated till now. This prompts future research with larger samples of patients, as the main limitation of our study is the low number of included MS subjects. The main reasons of this, is in our opinion, the inclusion criteria and probably for some MS centers, the logistic problems met by patients whose psychologist was accessible within the Hospital, compared with those who met the psychologist outside, in rehabilitation clinics. Centers whose neuropsychologist was easily accessible in rehabilitative structures had in fact greater inclusions and less drop outs. A future issue will be the possibility of structuring home based trainings, monitoring the effective practice by each patients, both in terms of correctness and of number of exercises performed at home. This could give additional interesting data on the effects of intensive cognitive rehabilitation in MS.

Another limitation of this study is the type of the control aspecific treatment. Although in randomized clinical trials dealing with neuropsychological rehabilitation, a psychological control treatment is difficult to be set and deserves intrinsic

TABLE 4 | Comparison of neuropsychological tests median raw scores at baseline (T0), after 1 year rehabilitation (T12) and after 2-years rehabilitation (T24).

	AG (*n* = 17)			SG (*n* = 15)			T 24: AG vs. SG
	T0	T12	T24	T0	T12	T24	*p*-value*
PASAT3	37	36	38	36	45	44	0.1619
PASAT2	23	29	30	24	35	32	0.1302
SPART10/36	18	19	19	15	22	21	0.1497
SPARTDR	6	6	5	4	7	7	0.0559
SRTLTS	33	40	37	30	44	46	0.2487
SRTCLTR	24	28	26	23	34	33	0.5966
SRTDR	8	8	8	7	9	8	0.7741
SDMT	40	40	35	44	49	46	0.0256
COWAL	28	30	30	34	35	35	0.0068
COWAC	40	42	41	38	42	45	0.3155
Stroop	20	27	25	23	30	30	0.1441

Mann Whitney test. Between groups comparison (*) at T24.

limitation, it is overtly recognized to be useful and recommended as a comparator treatment (Rosti-Otajärvi and Hämäläinen, 2014). The intrinsic limitation of a non domain specific psychological control treatment relies mainly in the fact that patients submitted to it may well have become aware of the psycho educational nature of this treatment, and may have consciously or unconsciously inferred that they were receiving the placebo treatment. This, in the specific case of our study, may have mainly impact the subjective perception of cognitive improvement we found in AG, more than the objective neuropsychological evaluation at follow ups.

In this study, similarly to others (Hämäläinen and Rosti-Otajärvi, 2014; Chiaravalloti and DeLuca, 2015) not only objective neuropsychological tests, but also subjective perception of the patients' cognitive improvement was measured. Patients in the SG subjectively perceived higher improvement in cognitive abilities than AG, although the scale we used was relatively simple and in the future better functional scales are welcome.

In conclusion, despite some limits, this is the first study evaluating the persistence of the cognitive improvement induced by a domain specific cognitive rehabilitation in MS with a follow up of 2 years. Despite limitations, results interestingly show a significant effect of this treatment in a multi center setting and its persistence after 2 years.

AUTHOR CONTRIBUTIONS

FM: Principal investigator, study design, results interpretation, manuscript writing and revision. CM and BC: Statistical analysis of the data. CS: Data collection from all the Centers and patients' evaluation in Brescia Center. FB: Treating psychologist in Brescia. RC: Patients selection in Brescia. AU, MP: Patients selection, patients evaluation and treatment in Genova. LP, LC: Patients selection, patients evaluation and treatment in Ancona. PG, AR: Patients selection, patients evaluation and treatment in Padova. GS, GF: Patients selection, patients evaluation and treatment in Sondrio. MP, BA: Patients selection, patients evaluation and treatment in Fidenza. RC, AL: Patients selection, patients evaluation and treatment in Como. MRT, CC: Patients selection, patients evaluation and treatment in Ferrara. AG, MR: Patients selection, patients evaluation and treatment in Gallarate. We thank Fondazione Cesare Serono for research suport.

REFERENCES

Amato, M. P., Goretti, B., Viterbo, R. G., Portaccio, E., Niccolai, C., Hakiki, B., et al. (2014). Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult. Scler.* 20, 91–98. doi: 10.1177/1352458513501571

Amato, M. P., Langdon, D., Montalban, X., Benedict, R. H., DeLuca, J., Krupp, L. B., et al. (2013). Treatment of cognitive impairment in multiple sclerosis: position paper. *J. Neurol.* 260, 1452–1468. doi: 10.1007/s00415-012-6678-0

Amato, M. P., Portaccio, E., Goretti, B., Zipoli, V., Ricchiuti, L., De Caro, M. F., et al. (2006a). The Rao's brief repeatable battery and stroop test: normative values with age, education and gender corrections in an italian population. *Mult. Scler.* 12, 787–793. doi: 10.1177/1352458506070933

Amato, M. P., Zipoli, V., and Portaccio, E. (2006b). Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal study. *J. Neurol. Sci.* 245, 41–46. doi: 10.1016/j.jns.2005.08.019

Barbarotto, R., Laiacona, M., Frosio, R., Vecchio, M., Farinato, A., and Capitani, E. (1998). A normative study on visual reaction times and two stroop colour-word tests. *Ital. J. Neurol. Sci.* 19, 161–170. doi: 10.1007/bf00831566

Calabrese, P. (2006). Neuropsychology of multiple sclerosis-an overview. *J. Neurol.* 253, I10–I15. doi: 10.1007/s00415-006-1103-1

Chiaravalloti, N. D., and DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 7, 1139–1151. doi: 10.1016/S1474-4422(08)70259-X

Chiaravalloti, N. D., and DeLuca, J. (2015). The influence of cognitive dysfunction on benefit from learning and memory rehabilitation in MS: a sub-analysis of the MEMREHAB trial. *Mult. Scler.* 21, 1575–1582. doi: 10.1177/1352458514567726

Chiaravalloti, N. D., Moore, N. B., Nikelshpur, O. M., and DeLuca, J. (2013). An RCT to treat learning impairment in multiple sclerosis: the MEMREHAB trial. *Neurology* 81, 2066–2072. doi: 10.1212/01.wnl.0000437295.97946.a8

Duque, B., Sepulcre, J., Bejarano, B., Samaranch, L., Pastor, P., and Villoslada, P. (2008). Memory decline evolves independently of disease activity in MS. *Mult. Scler.* 14, 947–953. doi: 10.1177/1352458508089686

Ernst, A., Blanc, F., De Seze, J., and Manning, L. (2015). Using mental visual imagery to improve autobiographical memory and episodic future thinking in relapsing-remitting multiple sclerosis patients: a randomised-controlled trial study. *Restor. Neurol. Neurosci.* 33, 621–638. doi: 10.3233/RNN-140461

Faul, F., Erdfelder, E., Lang, A. G., and Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/bf03193146

Fink, F., Rischkau, E., Butt, M., Klein, J., Eling, P., and Hildebrandt, H. (2010). Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial. *Mult. Scler.* 16, 1148–1151. doi: 10.1177/1352458510375440

Goretti, B., Patti, F., Cilia, S., Mattioli, F., Stampatori, C., Scarpazza, C., et al. (2014). The Rao's brief repeatable battery version B: normative values with age, education and gender corrections in an Italian population. *Neurol. Sci.* 35, 79–82. doi: 10.1007/s10072-013-1558-7

Hämäläinen, P., and Rosti-Otajärvi, E. (2014). Is neuropsychological rehabilitation effective in multiple sclerosis? *Neurodegener. Dis. Manag.* 4, 147–154. doi: 10.2217/nmt.14.8

Hubacher, M., Kappos, L., Weier, K., Stöcklin, M., Opwis, K., and Penner, I. K. (2015). Case-based fMRI analysis after cognitive rehabilitation in MS: a novel approach. *Front. Neurol.* 6:78. doi: 10.3389/fneur.2015.00078

Jønsson, A., Korfitzen, E. M., Heltberg, A., Ravnborg, M. H., and Byskov-Ottosen, E. (1993). Effects of neuropsychological treatment in patients with multiple sclerosis. *Acta Neurol. Scand.* 88, 394–400. doi: 10.1111/j.1600-0404.1993.tb05366.x

Kos, D., Nagels, G., D'Hooghe, M. B., Duportail, M., and Kerckhofs, E. (2006). A rapid screening tool for fatigue impact in multiple sclerosis. *BMC Neurol.* 6:27. doi: 10.1186/1471-2377-6-27

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33, 1444–1452. doi: 10.1212/WNL.33.11.1444

Mattioli, F., Flavia, M., Stampatori, C., Zanotti, D., Parrinello, G., and Capra, R. (2010a). Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. *J. Neurol. Sci.* 288, 101–105. doi: 10.1016/j.jns.2009.09.024

Mattioli, F., Stampatori, C., Bellomi, F., Capra, R., Rocca, M., and Filippi, M. (2010b). Neuropsychological rehabilitation in adult multiple sclerosis. *Neurol. Sci.* 31, S271–S274. doi: 10.1007/s10072-010-0373-7

Mattioli, F., Stampatori, C., Bellomi, F., Danni, M., Compagnucci, L., Uccelli, A., et al. (2015). A RCT comparing specific intensive cognitive training to aspecific psychological intervention in RRMS: the SMICT study. *Front. Neurol.* 5:278. doi: 10.3389/fneur.2014.00278

Mattioli, F., Stampatori, C., Scarpazza, C., Parrinello, G., and Capra, R. (2012). Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis. *Mult. Scler. Relat. Disord.* 1, 168–173. doi: 10.1016/j.msard.2012.06.004

Montgomery, S. A., and Asberg, M. (1979). A new depression scale designed to be sensitive to change. *Br. J. Psychiatry* 134, 382–389. doi: 10.1192/bjp.134.4.382

Plohmann, A. M., Kappos, L., Ammann, W., Thordai, A., Wittwer, A., Huber, S., et al. (1998). Computer assisted retraining of attentional impairments in patients with multiple sclerosis. *J. Neurol. Neurosurg. Psychiatr.* 64, 455–462. doi: 10.1136/jnnp.64.4.455

Pompeii, L. A., Moon, S. D., and McCrory, D. C. (2005). Measures of physical and cognitive function and work status among individuals with multiple sclerosis: a review of the literature. *J. Occup. Rehabil.* 15, 69–84. doi: 10.1007/s10926-005-0875-y

Poser, C. M., and Brinar, V. V. (2001). Problems with diagnostic criteria for multiple sclerosis. *Lancet* 358, 1746–1747. doi: 10.1016/s0140-6736(01)06842-8

Prakash, R. S., Snook, E. M., Lewis, J. M., Motl, R. W., and Kramer, A. F. (2008). Cognitive impairments in relapsing-remitting multiple sclerosis: a meta-analysis. *Mult. Scler.* 14, 1250–1261. doi: 10.1177/1352458508095004

Putzki, N., Fischer, J., Gottwald, K., Reifschneider, G., Ries, S., Siever, A., et al. (2009). Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur. J. Neurol.* 16, 713–720. doi: 10.1111/j.1468-1331.2009.02572.x

Rosti-Otajärvi, E. M., and Hämäläinen, P. I. (2014). Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database Syst. Rev.* 2:CD009131. doi: 10.1002/14651858.CD009131

Rosti-Otajärvi, E., Mäntynen, A., Koivisto, K., Huhtala, H., and Hämäläinen, P. (2013). Neuropsychological rehabilitation has beneficial effects on perceived cognitive deficits in multiple sclerosis during nine-month follow-up. *J. Neurol. Sci.* 334, 154–160. doi: 10.1016/j.jns.2013.08.017

Serino, A., Ciaramelli, E., Di Santantonio, A., and Ládavas, E. (2006). A rehabilitative program for central executive deficits after traumatic brain injury. *Brain Cogn.* 60, 213–214.

Solari, A., Filippini, G., Mendozzi, L., Ghezzi, A., Cifani, S., Barbieri, E., et al. (1999). Validation of Italian multiple sclerosis quality of life 54 questionnaire. *J. Neurol. Neurosurg. Psychiatr.* 67, 158–162. doi: 10.1136/jnnp.67.2.158

Sprague, S., Matta, J. M., Bhandari, M., Dodgin, D., Clark, C. R., Kregor, P., et al. (2009). Multicenter collaboration in observational research: improving generalizability and efficiency. *J. Bone Joint Surg. Am.* 91, 80–86. doi: 10.2106/jbjs.h.01623

Thomas, P. W., Thomas, S., Hillier, C., Galvin, K., and Baker, R. (2006). Psychological interventions for multiple sclerosis. *Cochrane Database Syst. Rev.* 1:CD004431. doi: 10.1002/14651858.cd004431.pub2

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GCG and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 29 February 2016
doi: 10.3389/fnbeh.2016.00034

Group Intensive Cognitive Activation in Patients with Major or Mild Neurocognitive Disorder

Simonetta Panerai[1], Domenica Tasca[1], Sabrina Musso[1], Valentina Catania[1], Federica Ruggeri[1], Alberto Raggi[2], Stefano Muratore[1], Giuseppina Prestianni[1], Cinzia Bonforte[1] and Raffaele Ferri[3]*

[1] Unit of Psychology I. C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy, [2] Unit of Neurology, Morgagni-Pierantoni Hospital, Forlì, Italy, [3] Unit of Neurology I. C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy

Background: No standard protocols are available for cognitive rehabilitation (CR) in conditions like Major or Mild Neurocognitive disorder (M-NCD or m-NCD, respectively); however, preliminary data seem to indicate that such interventions might have cost-effective beneficial effects and are free from side effect or adverse events. Three basic approaches are known: cognitive stimulation (CS), cognitive training (CT), and CR.

Objective: Aim of this study was to assess the efficacy of a protocol of group intensive cognitive activation (g-ICA) in patients with both M-NCD and m-NCD; the protocol was specifically arranged in our Research Institute, based on the principles of the central role of the patient and the mediation pedagogy.

Subjects and Methods: Sixteen patients with M-NCD and fifteen patients with m-NCD were enrolled, as well as eleven patients with M-NCD who were used as a control group (CG). The intervention was carried-out by a clinical neuropsychologist with daily group sessions over a period of 2 months. Neuropsychological assessment was performed at baseline and after the completion of the rehabilitative intervention.

Results: General cognitive functioning, attention, ideomotor praxis and visual memory scores were found to be significantly increased in all patients. Beneficial and significant effects were also found for constructive praxis in M-NCD and for executive functioning in m-NCD. All areas of the language function were significantly ameliorated in m-NCD, while this happened only for verbal repetition and syntax-grammar comprehension in M-NCD. No changes were detected for long- and short-term verbal memory, which were found to be worsened in controls without activation.

Conclusion: Our findings seem to indicate that g-ICA might be effective in inducing beneficial changes on the general cognitive functioning and other specific functions in patients with both m-NCD and M-NCD. Moreover, the specific protocol proposed, even if susceptible of important improvement, is easy to carry out within hospital facilities and cost-effective.

Keywords: cognitive stimulation, cognitive training, dementia, mild cognitive impairment, patient-focused cognitive intervention

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Pietro Cipresso, IRCCS Istituto Auxologico Italiano, Italy
Marina Zettin, Centro Puzzle, Italy

****Correspondence:***
Simonetta Panerai
spanerai@oasi.en.it

Received: *11 April 2015*
Accepted: *14 February 2016*
Published: *29 February 2016*

Citation:
Panerai S, Tasca D, Musso S, Catania V, Ruggeri F, Raggi A, Muratore S, Prestianni G, Bonforte C and Ferri R (2016) Group Intensive Cognitive Activation in Patients with Major or Mild Neurocognitive Disorder. Front. Behav. Neurosci. 10:34. doi: 10.3389/fnbeh.2016.00034

INTRODUCTION

The Statistical Manual of Mental Disorders—fifth edition (DSM-5; American Psychiatric Association, 2013) provides the new cluster of neurocognitive disorders which includes three syndromes: delirium, mild, and major neurocognitive disorders (m-NCD and M-NCD respectively). M-NCD is largely synonymous with dementia, although the criteria have been modified so that impairments in memory or learning are not essential for the diagnosis, except for NCD due to Alzheimer's disease (AD). M-NCD is characterized by the evidence of significant acquired deficits in one or more cognitive domains, based on concerns reported by the individual or the informants and preferably documented by standardized neuropsychological testing or quantified clinical assessment; such deficits must interfere with independence in everyday activities. m-NCD is synonym for mild cognitive impairment (MCI) and is characterized by a mild acquired cognitive decline not interfering with independence in everyday activities, even though greater effort or compensatory strategies may be required. The reason for diagnosing m-NCD resides in the increasing interest in early diagnosis and intervention to prevent or postpone dementia, although m-NCD is not always a precursor of dementia (Langa and Levine, 2014).

The DSM-5 also describes criteria for the diagnosis of specific etiological subtypes of both NCDM-NCD and m-NCD, based on their clinical features and biomarkers (e.g., Frontotemporal lobar degeneration, Traumatic Brain Injury, AD, Vascular Disease, Lewi body Disease, and Parkinson's Disease), and consistent with those developed by various expert groups. Nevertheless, establishing the etiology in m-NCD is rather difficult and may remain unspecified in many patients. For some etiologies, the level of certainty is also well defined, with "probable" representing a higher level of certainty than "possible" (for a review of NCD, see Sachdev et al., 2014).

Options for treating M-NCD include both pharmacological and non-pharmacological therapies. At present, no drugs capable of modifying the disease and totally control the symptoms are available (Hildreth and Church, 2015); therefore, cognitive interventions have been gradually and increasingly focused as an emerging therapeutic approach which could aid prevention and treatment of dementia, especially combined with exercise and pharmacological therapy (Loewenstein et al., 2004; Law et al., 2014). The hypothesis that persons with neurocognitive diseases might benefit from cognition-based intervention derives from the concepts of neuronal plasticity and cognitive reserve and from a general view that the lack of cognitive activity hastens cognitive decline, in normal ageing individuals as well as those with dementia. However, according with some studies, deterioration cannot be stopped after 2 years of treatment in patients with dementia (Requena et al., 2006; Woods et al., 2012). Another study by Jedrziewski et al. (2014) carried out with community-resident and institutionalized persons, showed that engagement in cognitive activities was inversely associated with the onset of cognitive impairment at 5-year follow-up, but was no longer significant at 10-year follow-up, this resulting in the fact that cognitive interventions possibly lower the risk for cognitive impairments and dementia and might delay their onset.

Neural plasticity can be defined as the ability of the nervous system to adapt its structural organization in response to factors affecting its integrity and functioning. Protecting neural plasticity in brain regions typically affected in AD might improve the neurological functioning and prevent the loss of neuronal processes that occur in this disease (Buschert et al., 2010). Neural plasticity also plays a role in cognitive reserve which represents the brain's ability to make flexible and efficient use of cognitive networks when performing tasks in the presence of brain pathology (Stern, 2002). Persons with higher cognitive reserve tend to have better clinical outcomes for any level of pathology and brain reserve (Stern, 2013). Among all the factors influencing cognitive reserve, mentally stimulating activities were shown to have the largest effect on the risk for dementia and might attenuate cognitive decline. Therefore, cognitive interventions could potentially delay the onset of dementia, as in the case of m-NCD, attenuate the clinical symptoms associated with M-NCD and partially reduce the speed of decline (Buschert et al., 2010). As compared with pharmacological treatment, cognitive intervention appears to be less expensive and more cost-effective (Buschert et al., 2010) and free from side effects or adverse events.

However, research in this area is rather scarce and evidence of effectiveness rather controversial (Alves et al., 2013); moreover, to date, no standard protocols are available for cognitive intervention in conditions such as M-NCD or m-NCD. Three main cognition-based approaches emerge from the literature: cognitive stimulation (CS), cognitive training (CT) and cognitive rehabilitation (CR; Clare and Woods, 2004; Buschert et al., 2010; Alves et al., 2013; Choi and Twamley, 2013).

CS includes a range of group activities with the aim to enhance general cognition and social functioning. This approach assumes that cognitive functions work together and should be stimulated at the same time in a social setting. CS is based on reality orientation (RO), first described (Taulbee and Folsom, 1966) as a technique to improve the quality of life of confused elderly people, although its origins lie in an attempt to rehabilitate severely disturbed war veterans. RO involves the presentation of orientation and memory information, relating, for example, to time, place, and person, in order to provide the person with a greater understanding of his/her surroundings, possibly resulting in an improved sense of control and self-esteem. The basic principles of RO have been incorporated in the everyday clinical practice and in new formats of treatments. Of notice, the cognitive stimulation therapy (CST), by Spector et al. (2003), a brief group intervention (14 person-centered sessions of themed enjoyable activities), designed for patients with dementia, has received evidence of its efficacy on cognitive functions and quality of life (Woods et al., 2012). CST seem to be independent of whether people are taking acetylcholinesterase inhibitor (AChEI) medication, and that being older or female implies increased cognitive benefits from the intervention; care home residents improve more than community residents on quality of life, but the community sample seems to improve more in relation to behavior problems. This method has been published as a manual (Spector et al., 2006) and is the only non-pharmacological intervention recommended by the National Institute for Health and Clinical Excellence (2007) for the treatment of cognitive symptoms in dementia. It also appears to be cost-effective (Knapp et al., 2006).

CT is an approach consisting of computer-based or paper-and-pencil cognitive exercises with different levels of difficulty, targeting specific cognitive functions (e.g., attention, memory, problem-solving). It is performed individually or in group, with the aim to enhance targeted functions and teach compensatory techniques, generalizable to daily life. There is evidence, in pre-dementia and mild-to-moderate AD, of cognitive improvements (Cipriani et al., 2006; Talassi et al., 2007), but not of generalization (see Alves et al., 2013). CT is especially employed with MCI patients, mainly focusing on episodic memory, but also on attention, executive functions, language, visual-spatial abilities and processing speed (Simon et al., 2012). Computerized CT did not show higher improvements when compared to non-computerized training. CT also includes restorative (such as errorless learning, spaced retrieval, errorful learning, reminiscence therapy) and compensatory strategy (such as visual imagery, method of loci, mind mapping, cueing, external memory aids), frequently applied simultaneously. The results from different studies are rather inconsistent with regard to the enhancement of memory domain and generalization to other cognitive functions (Simon et al., 2012). A recent meta-analysis of randomized controlled trials by Wang et al. (2014) found significant effects on global cognitive functions, and weak evidence of improvements in executive functions and delayed memory. Very briefly, CST appears to be more effective in patients with dementia (Yuill and Hollis, 2011), whereas CT seems to be more effective in patients with MCI (Buschert et al., 2010).

CR is an individualized approach, which employs any intervention strategies that might enable patients and their families to manage cognitive deficits, considered within the interaction between the patient and the environment. The main difference between this approach and the CT is the full involvement of the family in the treatment. Compensatory methods, verbal instructions and physical demonstrations are used (Choi and Twamley, 2013). To date, there are very few studies about this approach and evidence of CR benefits is still to be obtained (Alves et al., 2013).

Other non-pharmacological multicomponent approaches are described in the literature that substantially appear to be variations of CT, for example interventions combining CT with RO (Raggi et al., 2007), with physical exercises and CS (Olazarán et al., 2004), with activities of daily living (ADL; Avila et al., 2004), or with transcranial magnetic stimulation (Bentwich et al., 2011). Some authors (Yamaguchi et al., 2010; Yamagami et al., 2012), shifting from "what" is taken to "how" it is taken, suggested a combined treatment, that is the brain-activating rehabilitation (BAR), based on five principles: enjoyable activities in an accepting atmosphere, empathetic communication between patients as well as between the therapist and the patients, enhancing motivation by means of praises, conferring a social role to each patient (based on his/her remaining abilities), errorless learning in order to maintain the patient's dignity; evidence of a decreased social withdrawal and global severity of dementia was provided by a randomized clinical trial but no difference was found in cognitive tests.

In summary, taken as a whole, previous studies show evidence for small but consistent effects of non-pharmacological cognitive interventions in improving global cognitive functions in patients with both MCI or dementia, especially AD. At present, however, no standardized intervention programs have been designed yet and research in this field "is still in its infancy, and in spite of the growing evidence of its effectiveness, is still lacking recognition among health professionals as well as caregivers" (Alves et al., 2013). Therefore, the search for additional evidence concerning the efficacy of these approaches for each type of dementia and deterioration stages is strongly recommended. Considering that the worldwide number of patients with dementia is expected to dramatically increase, the need to implement cognitive interventions in inpatient and outpatient services for subjects with NCD has become more and more compelling.

The aim of this article is to report preliminary results on the implementation of the group intensive cognitive activation (g-ICA), a combined treatment properly designed in our Research Institute, and delivered in an inpatient hospital setting to persons with M-NCD and m-NCD, on the basis of their cognitive outcomes. This approach represents a proposal aimed at the enrichment of the traditional rehabilitation programs provided in hospitals, generally based on physical and language therapy.

MATERIALS AND METHODS

Participants

The patient group included 16 subjects (6 males and 10 females) with mild-to-moderate M-NCD and 15 patients with m-NCD (7 males and 8 females), diagnosed on the basis of the DSM-5 criteria by a multidisciplinary team (including a senior geriatrician, a neurologist, and a psychologist) before their admission at the Rehabilitation Unit of our Institute. As far as the M-NCD sample is concerned, in seven patients the disease was due to possible AD, in three to vascular disease, in three to frontotemporal lobar degeneration-language variant, in one to frontotemporal lobar degeneration-behavioral variant, and in one to traumatic brain injury. Patients with M-NCD due to possible AD were treated with cholinesterase inhibitors soon after the completion of the diagnostic process. Within the m-NCD sample, in six patients the disease was due to possible AD, in five to vascular disease, in two to traumatic brain injury and in two to another medical condition (namely removal of benign brain tumors). Mean chronological age of patients with M-NCD was 64 years (±10.64 SD); early onset of the diseases (<65 years) was evident in 11 individuals. Mean chronological age of patients with m-NCD was 57 years (±9.82 SD). Patients with M-NCD were assigned to treatment groups on the basis of the severity of the disorder (mild or moderate) following the waiting list; patients with m-NCD were assigned to treatment groups following the waiting list.

Inclusion criteria to be met for M-NCD were as follows: (a) DSM-5 diagnostic criteria for M-NCD; (b) score between 10 and 23 at the mini mental state examination (MMSE; Folstein et al., 1975); (c) score between 40 and 85 (mild or moderate cognitive decline) at the milan overall dementia assessment (MODA; Brazzelli et al., 1994); (d) score between 1 and 2 at the clinical dementia rating (CDR; Hughes et al., 1982); (e) loss of almost one ADL (Katz et al., 1970) and/or instrumental activities of daily living (IADL; Lawton and Brody, 1969); and (f) patients presented with some communication abilities, no major sensorial (sight and hearing) or physical illnesses and no behavioral problems impairing their participation to group activities. Inclusion criteria to be met for m-NCD were as follows: (a) DSM-5 diagnostic criteria for m-NCD; (b) score between 24 and 26 at the MMSE; (c) score between 85.5 and 89 (borderline cognitive level) at the MODA; (d) score 0.5 at CDR; (e) ADL and IADL globally maintained; and (f) patients had no major sensorial (sight and hearing) or physical illnesses impairing their participation to group activities.

A control group (CG) was also recruited which included 11 elderly with M-NCD (2 males and 9 females) who received daily care and assistance, with daily animation activities and weekly attendance of religious events. Their mean age was 69 years (±7.87 SD). Inclusion criteria were: (a) score between 10 and 23 at the MMSE (Folstein et al., 1975); (b) score between 40 and 85 (mild or moderate cognitive decline) at the MODA (Brazzelli et al., 1994); (c) score between 1 and 2 at the CDR (Hughes et al., 1982); and (d) loss of almost one ADL (Katz et al., 1970) and/or IADL (Lawton and Brody, 1969).

Procedures

g-ICA is an intensive combined group treatment including 30 cognitive activation sessions, delivered by a trained clinical neuropsychologist, supported by a practicing psychologist. A pre/post neuropsychological assessment was administered to all groups of patients.

Also for CG, two neuropsychological battery administrations were carried out, the last after 2 months from the first. CG did not benefit from the g-ICA program.

The neuropsychological battery and the arrangement of sessions and contents are described in the following paragraph.

Neuropsychological Instruments

In order to overcome the weaknesses typically deriving from only one or two measures of the global cognitive functioning and with the aim of obtaining a wide-spectrum neuropsychological profile, a comprehensive neuropsychological battery was used, as suggested by Bianchi and Dai Prà (2008). Global cognitive functioning was evaluated by means of a number of measures, and namely the MMSE (Folstein et al., 1975), the MODA (Brazzelli et al., 1994), and the montreal cognitive assessment (MoCA, Nasreddine et al., 2005); to assess reasoning ability and intellectual level, the colored progressives matrices (CPM; Basso et al., 1987) were used; short term memory was assessed by means of the Digit Span (Orsini et al., 1987), the Serial repetition of two-syllable words (Spinnler and Tognoni, 1987), and test of Corsi (Orsini et al., 1987); verbal episodic memory (immediate and delayed recall) was investigated by means of the Rey's 15 words (Carlesimo et al., 1996); non-verbal episodic memory by the Enhanced Cued Recall (Grober et al., 1988) and the Rey's Complex Figure-memory reproduction (Carlesimo et al., 2002); selective attention was evaluated using the Digit Cancellation test (Spinnler and Tognoni, 1987); for the spatial cognition and constructional apraxia the copy of Rey's Complex Figure (Caffarra et al., 2002) was used; ideomotor praxis was assessed by means of the Imitating Gestures Test (De Renzi et al., 1980); for the assessment of the language abilities, the Aachener Aphasia Test (Italian version) was employed (Luzzatti et al., 1996) and for the frontal functions, the frontal assessment battery (FAB; Dubois et al., 2000).

The g-ICA Protocol

The g-ICA protocol is based on two general principles: the central role of the patient and the mediation pedagogy. The patient-centered principle consists in taking into account the patients' needs and expectations. Patients with dementia are commonly willing to improve their health condition, maintain their cognitive and daily-living abilities while minimizing any memory loss; moreover, they need to be listened to, and receive emotional support (Bossen et al., 2009). Consequently, g-ICA was properly designed to include activities tapping on a wide spectrum of cognitive abilities, which appeal to the cognitive strength of patients, bringing them out of a vicious circle of failure toward a new virtuous circle based on capabilities and abilities. The principle of the mediation pedagogy comes from the theory of Structural Cognitive Modifiability which is, in practice, the mediated learning experience (Feuerstein, 1999). In our approach, mediation is focused on interpersonal relationships, characterized by a loop of dynamic and positive feedbacks between patients and the mediator; this latter, in a respectful and pleasant atmosphere, essentially encourages the patients—never standing in for them—to engage with stimuli and provides the required prompts, so they can actively and successfully complete the task. The mediator is required to show empathy, sense of humor and the ability to make cognitive activities as pleasant as possible. A package of proactive (antecedent) and reactive (consequent) procedures (Cooper et al., 2007) is used, in order to raise the patients' motivation in the working area and during cognitive activities, and maintain self-esteem; namely: a prosthetic physical environment, made of a separate and comfortable room, equipped with a calendar, a wall clock and other visual cues, a computer, a video projector and a whiteboard; a 20 min break with a snack; errorless learning (prompts, prompt-fading and delayed prompt); variation of activities and materials; variation of task difficulties; use of social positive reinforcements; correction of errors, by highlighting positive aspects of the response and adding new stimuli aimed to lead patients to independently overview the global quality of their response.

The g-ICA is an intensive group treatment combining CS (including RO) and CT; in our setting, each group was made

TABLE 1 | Weekly plan of activities in g-ICA.

Day	Cognitive functions stimulated	Activities examples for participants with M-NCD	Activities examples for participants with m-NCD
Every day	Global	Reality orientation (day, month, year, season, weather, time estimate, name of participants, building one's own identity card and other personal information, temporal and spatial relations)	Reality orientation (date; mental calculations-hours and days within a month, a season or a year)
	Ecological memory	Memory in the boxes: group game with personal objects; this game was taken from Florenzano (1988) and then adapted	Memory in the boxes (group game with neutral objects)
Monday/Thursday	Ideomotor praxis	Each participant, in turn, moves a part of his/her body (right or left); the other participants have to imitate the movement (right and left, accordingly); variations can include different number of repetitions and imitation of two series of movements	Each participant, in turn, moves a part of his/her body (right or left); the other participants have to imitate the movement (right and left, accordingly); variations can include imitation of three or more series of movements forward and backward
Monday/Friday	Global	Getting pairs of cards (it is a group card game; each set contains paired cards on established themes—such as food, objects, clothes, etc.; each participant receives 6–8 cards and is required to reconstruct the highest number of pairs following certain rules)	Getting pairs of cards (in this case, cards have to be paired not only on the basis of their sameness, but also on the basis of logical matching; each player can receive up to 20 cards)
	Visual, auditory and spatial memory	Little computerized and non-computerized memory games for adults (shapes, cards, black and white figures, flags, faces, colors, numbers, letters, smiles, word retrieval, sentences repetition, location of objects, etc.)	Big computerized and non-computerized memory games for adults
Tuesday/Thursday	Auditory and visual selective attention	Computerized and non-computerized non-verbal cancelation tasks/sounds and words recognition (one or two meaningful target stimuli)	Computerized and non-computerized non-verbal cancelation tasks/sounds and words recognition (two or more meaningful or non-meaningful target stimuli)
	Global	Functional tasks (telling time, counting money, using a calendar, reading simple instructions, using the mobile phone, etc.)	Functional tasks (solving daily math problems, understanding medicine labels, writing a phone message, using the internet, etc.)
Tuesday/Friday	Verbal language	Naming (objects, pictures, features, functions, classes); pictures description; sentences repetition; reading, comprehension, reconstruction of a brief story through pictures and written sentences; creating a story II (guided group play)	Sentences repetition; verbal fluency; verbal inference; creating a story I (each participant adds a new sentence at a time, keeping a logic sequence of the story events); creating a story II (guided work play).
Wednesday	Constructional praxis	Drawing tasks (figure copy or completion); easy tangrams; cubes or matches constructions	Tangrams; identify and outline given figures within a cloud of dots; differentiating (divide a whole into its parts) and integrating (join parts into a whole); computerized and non computerized stencil design (through superimposed parts).
	Semantic memory	Starting from a central topic, all related information were retrieved by using a fixed diagram including category, environment, features, functions and free associations (Celentano et al., 2002)	
	Ecological problem solving	Starting from a visual presentation of a everyday problem situation, participants are required to express what they think about the situation and what they would do (tasks adapted from Schwartz, 1990, 1993).	Starting from a verbal presentation of a everyday problem situation, participants are required to analyze the situation, hypothesize the antecedents and the purposes of the characters, and finally to express what they think about the situation and what they would do

of four/five participants. Interventions were delivered in an inpatient hospital setting, with daily group sessions, each lasting approximately 3.5 h, 5 days a week (from Monday to Friday), over a period of 2 months. During the first and the last weeks, neuropsychological assessments were administered; cognitive activation sessions extended over a period of 6 weeks. Each session begun with the mediator welcoming the patients, then engaging in a little discussion about gossip/crime news recently happened or about facts that had taken place where patients resided; then, a short overview of the activities carried out in the last meeting was discussed and a RO activity (day, month, year, season, weather, time, name of participants) was started, followed by cognitive or non-cognitive tasks, a short break, and cognitive or non-cognitive tasks once again; finally, the overall course of the session and the level of engagement and feelings of patients were discussed. Contents were organized on a weekly basis, in order to stimulate a wide range of cognitive functions; the level of difficulty of the activities was adapted to the group cognitive capability (**Table 1**). Both paper-pencil and computer activities were employed to train specific cognitive functions.

Statistical Analysis

We first obtained descriptive statistics for all parameters measured in this study which served to calculate the Cohen's *d* value. Cohen's *d* is defined as the difference between two means divided by the pooled standard deviation for those means. According to Cohen, 0.2 is indicative of a small effect, 0.5 of a medium and 0.8 of a large effect size.

Most variables analyzed in this study did not show a normal distribution; for this reason, non-parametric statistics were subsequently used. Thus, the results obtained from the pre- and post-treatment assessments in both groups of patients and in both M-NCD subgroups were compared by means of the Wilcoxon test for paired data sets. Significance level was set as $p < 0.05$. However, as for each parameter four different comparisons were performed, also the Bonferroni correction was applied and the corresponding corrected significance level was set at $p < 0.0125$.

The comparison between the results of the first and second neuropsychological battery administration in the CG was carried out by means of the Wilcoxon test for paired data sets.

The comparison between the M-NCD group and controls was carried out by means of the Mann-Whitney U test. The significance level was set as $p < 0.05$.

Ethics Approval

This study was carried out in accordance with the Regulations of the Local Ethics Committee "Oasi Maria SS." (CE17/06/2013OASI) abiding by the National Regulations for Ethics Committees. Written informed consent was obtained by all volunteering subjects before entering the study, in accordance with the Declaration of Helsinki. The population involved in this study, albeit vulnerable, were able to personally give their consent to participate to the study. In case of patients with dementia, caregivers have been also informed about objectives and procedures of the research study.

RESULTS

Table 2 reports descriptive statistics and effect size of the results obtained in all groups of patients. The statistical significance of the difference between the results obtained from pre- and post-treatment assessments are reported in **Table 3**; the findings in m-NCD and M-NCD will be described separately.

Patients with M-NCD

Global cognition improved significantly, as indicated by the MODA and MMSE, in the whole sample as well as in both subgroups with and without AD. The whole sample and the group with M-NCD due to AD showed a statistically significant improvement also at the MoCA. When analyzing the sub-sessions of MODA, namely Orientations and Neuropsychological Tests, it must be noticed that all the groups improved in neuropsychological performance (M-NCD total sample: $p = 0.017$; M-NCD due to AD: $p = 0.018$; M-NCD non-AD: $p = 0.025$), whereas Orientations turned out to be improved in non-AD M-NCD only ($p = 0.008$).

No difference was found between pre- and post-treatment comparisons for reasoning ability, frontal functions and memory tests, except for the non-verbal Enhanced Cued Recall, in which a statistically significant difference was found in the whole sample (with a small Cohen's *d*) and in the M-NCD due to AD. Selective attention improved in the whole sample, whereas in the two sub-groups with and without AD changes did not reach statistical significance.

Statistically significant differences were found for language abilities in the whole sample; namely, for syntactic comprehension of sentences (Token test; with a small Cohen's *d*) and verbal repetition (but small Cohen's *d*); in the sub-group with M-NCD due to AD, for syntactic comprehension, ecological comprehension (with a small Cohen's *d*) and naming; and in the sub-group with M-NCD non-AD, for verbal repetition only.

Enhanced ideomotor praxis (Imitating Gestures test) was found in all the groups, whereas constructional praxis (Rey's Complex figure-copy) reached a statistical significance in the whole sample and in the M-NCD due to AD.

In summary, following the g-ICA treatment, patients with M-NCD, both the whole sample and the two sub-groups with and without AD, showed improvements in global cognitive function and ideomotor praxis. The sub-group with M-NCD due to AD showed improvements also in some verbal language domains, such as verbal comprehension and naming, in constructional praxis and delayed visual memory. The sub-group with M-NCD non-AD showed improvements in verbal repetition and orientations. Reasoning abilities, verbal memory and executive functions did not appear to be susceptible of improvements.

Patients with m-NCD

Patients with m-NCD showed statistically significant improvements in global cognitive functioning, reasoning, executive function, short term memory (digit span), delayed non-verbal memory (Rey's complex figure-memory reproduction), selective attention, ideomotor praxis, and in all language domains (namely, syntactic and ecological verbal comprehension of sentences, naming, written language), except for repetition.

Comparison between M-NCD and CG

The comparison between M-NCD and CG basically confirmed the results obtained from the comparison between the pre- and post-treatment assessments in patients with M-NCD (**Table 4**).

In fact, significant differences were found in the general cognitive functioning, in visual memory, selective attention, praxis, and in some language areas (syntactic verbal comprehension and repetition). Significant differences were obtained also in the visual-spatial reasoning (CPM), immediate verbal recall, frontal functions, naming, and written language.

DISCUSSION

The g-ICA is a short (6 weeks) combined intensive intervention based on mediation pedagogy and patient-centered principles. It is characterized by CS activities and cognitive tasks. Other multi-component approaches have been described in the literature (Avila et al., 2004; Olazarán et al., 2004, 2010; Sitzer et al., 2006; Raggi et al., 2007), usually implemented in patients with dementia. In our study, the combined treatment has also

TABLE 2 | Descriptive statistics and effect size of the results obtained in all groups of patients.

	M-NCD all (*n* = 16)			M-NCD due to possible AD (*n* = 7)			M-NCD not due to AD (*n* = 9)			m-NCD (*n* = 15)			CG (*n* = 11)		
	Mean	SD	Cohen's *d*	Mean	SD	Cohen's *d*	Mean	SD	Cohen's *d*	Mean	SD	Cohen's *d*	Mean	SD	Cohen's *d*
MODA															
Pre	67.55	10.07	0.66	74.74	4.23	1.68	61.25	9.51	0.66	81.71	6.82	1.18	76.93	8.22	0.47
Post	74.61	11.09		82.39	4.86		67.81	10.61		88.73	4.90		73.04	8.23	
MMSE															
Pre	15.80	4.26	0.83	18.63	2.07	1.39	12.97	4.05	0.91	24.29	2.66	0.73	20.37	2.02	0.90
Post	19.87	5.43		22.12	2.88		17.89	6.51		26.02	2.06		18.22	2.72	
MoCA															
Pre	11.78	5.17	0.55	14.40	2.97	0.97	8.50	5.80	0.43	19.5	5.58	0.96	Not administered		
Post	14.78	5.76		17.80	3.96		11.00	5.77		32.71	2.64		Not administered		
Colored progressive matrices															
Pre	18.19	6.63	0.54	18.63	4.15	0.67	17.80	8.53	0.55	26.11	5.01	0.67	18.95	2.77	0.77
Post	21.74	4.98		21.77	5.21		21.70	5.15		29.13	3.95		16.68	3.08	
Digit span															
Pre	3.80	1.35	0.32	4.68	0.98	0.76	3.03	1.17	0.11	3.83	1.18	0.26	4.59	0.38	0.56
Post	3.40	1.12		3.96	0.91		2.91	1.10		4.10	0.92		4.32	0.56	
Corsi's test															
Pre	3.38	1.22	0.11	3.07	0.97	0.30	3.66	1.42	0.33	3.43	1.27	0.29	4.32	0.76	0.12
Post	3.23	1.43		3.36	0.98		3.14	1.76		3.80	1.29		4.23	0.69	
Serial repetition of two syllabic words															
Pre	2.55	0.79	0.21	2.96	0.51	0.52	2.19	0.84	0.10	2.73	0.86	0.71	3.66	0.39	0
Post	2.75	1.10		3.25	0.60		2.31	1.28		3.33	0.84		3.66	0.39	
Rey's 15 words-immediate recall															
Pre	22.94	8.35	0.11	26.63	8.28	0.10	19.71	7.42	0.26	34.82	5.75	0.58	28.99	6.47	0.67
Post	23.81	8.38		25.91	6.46		21.96	9.81		39.18	8.91		25.15	6.84	
Rey's 15 Words-delayed recall															
Pre	2.93	3.25	0.09	3.91	2.94	0.008	2.08	2.23	0.26	6.71	2.51	0.53	4.85	2.25	0.16
Post	2.66	2.31		3.89	2.14		2.69	2.44		8.19	3.03		4.47	2.59	
Rey complex figure-memory reproduction															
Pre	6.78	6.82	0.21	2.20	1.68	0.96	12.50	6.45	0.37	13.75	5.69	0.40	4.32	3.47	0.16
Post	8.11	5.90		6.40	5.97		10.25	5.85		16.42	7.63		3.77	3.48	
Enhanced cued recall															
Pre	7.60	4.07	0.27	7.57	2.51	0.41	7.63	5.26	0.54	13.64	2.9	0.10	14.73	1.01	0.66
Post	8.67	3.85		8.71	3.09		8.63	4.63		13.93	2.87		13.73	1.90	
Digit cancellation test															
Pre	20.45	9.73	0.50	22.71	11.43	0.52	18.19	7.89	0.20	35.69	11.56	0.59	26.75	6.27	0.34
Post	25.60	10.95		27.82	8.11		23.66	11.84		41.98	9.62		24.45	7.14	

(Continued)

TABLE 2 | (Continued).

	M-NCD all (*n* = *16*)			M-NCD due to possible AD (*n* = 7)			M-NCD not due to AD (*n* = 9)			m-NCD (*n* = 15)			CG (*n* = 11)		
	Mean	**SD**	**Cohen's *d***	**Mean**	**SD**	**Cohen's *d***	**Mean**	**SD**	**Cohen's *d***	**Mean**	**SD**	**Cohen's *d***	**Mean**	**SD**	**Cohen's *d***
Imitating gestures test															
Pre	41.04	11.21	0.81	42.50	13.16	0.92	39.57	9.69	0.56	59.40	7.52	1.02	46.41	6.31	0.94
Post	50.01	10.88		53.29	10.25		45.40	11.08		65.63	4.26		40.82	5.59	
Rey complex figure-copy															
Pre	16.78	8.08	0.74	11.80	5.99	1.30	23.00	5.77	0.21	27.11	7.68	0.04	13.55	5.14	0.42
Post	21.94	5.75		20.30	7.03		24.00	3.49		27.43	9.68		11.41	5.08	
Frontal assessment battery															
Pre	8.10	3.70	0.35	10.40	3.91	0.29	5.80	1.48	0.82	12.33	3.37	1.02	10.36	3.20	0.27
Post	9.30	3.20		11.40	2.88		7.20	1.92		15.14	1.96		9.45	3.45	
AAT-Token test															
Pre	55.19	9.57	0.24	63.86	5.43	0.45	48.44	5.70	0.33	65.73	5.96	0.61	58.09	6.22	0.24
Post	57.56	10.52		66.71	7.11		50.44	6.27		68.93	4.46		56.45	7.61	
AAT-Repetition															
Pre	56.47	9.16	0.33	64.00	7.21	0.15	49.88	4.09	0.72	63.47	5.80	0.12	51.36	4.27	0.28
Post	59.69	10.23		65.14	7.99		55.44	10.10		64.50	10.05		50.18	4.31	
AAT-Written language															
Pre	57.88	9.27	0.15	63.86	8.90	0.28	53.22	6.78	0.08	68.27	5.82	0.32	54.36	4.72	0.12
Post	59.44	10.89		66.71	11.10		53.78	6.91		70.09	5.39		53.78	4.96	
AAT-Naming															
Pre	55.94	10.16	0.40	63.00	8.29	0.60	50.44	8.02	0.40	75.13	14.95	0.03	55.55	6.49	0.17
Post	60.38	12.05		68.29	9.25		54.22	10.53		72.50	10.50		54.45	6.38	
AAT-Comprehension															
Pre	52.63	7.37	0.23	57.00	7.59	0.29	49.22	5.36	0.23	64.79	8.29	0.27	51.55	4.95	0.12
Post	54.69	10.12		59.29	8.36		51.11	10.34		67.27	9.95		50.82	6.95	

TABLE 3 | Statistical significance of the differences between the results obtained from pre- and post-treatment evaluations in patients with m-NCD and M-NCD (Wilcoxon test).

	M-NCD all (*n* = 16) *p*	M-NCD due to possible AD (*n* = 7) *p*	M-NCD not due to AD (*n* = 9) *p*	m-NCD (*n* = 15) *p*
Global cognitive function				
MODA	0.005*	0.018	0.008*	0.015
MMSE	0.008*	0.018	0.028	ns
MoCA	0.021	0.043	ns	0.008*
Reasoning and cognitive level				
Colored progressive matrices	ns	ns	ns	0.024
Memory				
Digit span	ns	ns	ns	ns
Corsi's test	ns	ns	ns	ns
Serial repetition of two-syllabic words	ns	ns	ns	0.022
Rey's 15 words-immediate recall	ns	ns	ns	ns
Rey's 15 words-delayed recall	ns	ns	ns	ns
Rey's complex figure-memory reproduction	ns	ns	ns	0.007*
Enhanced cued recall	0.041	0.028	ns	ns
Selective attention				
Digit cancellation test	0.048	ns	ns	0.008
Praxis				
Imitating gestures test	0.002*	0.018	0.043	0.001*
Rey's complex figure-copy	0.044	0.043	ns	ns
Frontal functions				
Frontal assessment battery	ns	ns	ns	0.002
Language				
Aachener aphasia test (AAT)—Token test	0.006*	0.028	ns	0.019
AAT—Repetition	0.009*	ns	0.028	ns
AAT—Written language	ns	ns	ns	0.035
AAT—Naming	ns	0.043	ns	0.018
AAT—Comprehension	ns	0.043	ns	0.018

Significant after Bonferroni correction.

been implemented with m-NCD, due to the program flexibility and to customable tasks; furthermore, unlike other studies in the literature, in which results are usually described for AD or for patients with unspecified types of dementia (for a review see Alves et al., 2013), in our study results were also analyzed in the two sub-groups, with and without AD.

The whole M-NCD showed statistically significant improvements in almost all the investigated domains after treatment and most of these improvements were significantly higher than the changes observed in the CG in which worsening was the rule. As far as the global cognition is concerned, improvements were evident for the whole group with M-NCD and for both sub-groups (with and without AD); these positive modifications were found in all the global cognitive functioning batteries used, namely MoCA, MMSE and MODA, although *p* values were greater for MODA and MMSE than for MoCA: differences between *p* values might be ascribed to the fact that MoCA trials are more difficult than those included in the other two cognitive batteries, since MoCA enables to detect also a mild cognitive decline. These results are congruent with those from the literature, with regard to CS (Sitzer et al., 2006; Woods et al., 2012; Aguirre et al., 2013; Alves et al., 2013) and CT programs (Cipriani et al., 2006; Sitzer et al., 2006; Talassi et al., 2007; Alves et al., 2013), as well as to integrated programs (Olazarán et al., 2004). Our study also provides additional information about the global cognitive gains in patients with non-AD M-NCD. Moreover, the improved global cognition, indeed, seems to be more related to improvement in neuropsychological functioning and less to orientation for which, however, only patients with non-AD M-NCD showed a statistically significant improvement. These data might be explained by to the fact that orientation requires the use of memory, the cognitive function which first deteriorates in AD, in conjunction with attention and executive functioning (Traykov et al., 2007), and appears less susceptible of improvements following CS or training. In addition, from our study information about reasoning abilities and IQ—which were not improved—can also be derived: therefore, it can be hypothesized that improvements in global cognitive functioning are not related to increased IQ or reasoning abilities, but rather to more efficient cognitive functions as a whole. However, the comparison with the CG has shown a significant difference because the latter had a clear worsening; this might indicate that cognitive activation, even if was not able to improve the IQ, at least was able to maintain it at the pre-activation level; this was not true for the CG in which no activation was carried out.

Statistically significant results were obtained in Ideomotor praxis for all patients with M-NCD; this cognitive function has not usually been taken into account in the literature, despite the important role of motor components in the basic or instrumental daily living activities. Also for constructional praxis we found improved performance in the whole sample with M-NCD and in the sub-group with AD. Only marginal significance was found for changes in selective attention in the whole sample with M-NCD only; we believe that this result might be explained by the low power of our analysis due to its small sample size (a frequent methodological problem in rehabilitation studies) and this holds true for all the analyses we carried out.

In line with the results reported by the majority of studies in the literature (Alves et al., 2013; Choi and Twamley, 2013), no improvements in memory were found in our study, except for visual memory (Enhanced Cued Recall), in which a statistically significant result was obtained both for M-NCD as a whole (but with a small effect size) and M-NCD due to AD. This result is likely to be due to test administration and scoring, including induction of semantic processing, immediate cued recall four-by-four items, delayed free recall and delayed cued recall of all items; total scores included both free and cued recall (Grober et al., 1988), whereas, in the other memory tests, scores commonly include free recall only. As a whole, memory functions was very little improved; this result has an explanation in the early and severe memory deterioration in M-NCD, especially due to AD. The same applies for executive functions, in which no improvement was found. Nevertheless, the comparison between M-NCD and CG showed a statistically significant difference both in immediate verbal recall and in frontal functions: this result suggests that although g-ICA treatment did not cause

TABLE 4 | Results obtained from the comparison between M-NCD (n = 16) and CG (n = 11; Mann Whitney U test).

	M-NCD Δ means (±SD)	CG Δ means (±SD)	M-NCD vs. CG *p*
Global cognitive function			
MODA	7.07 (4.9)	3.89 (4)	<0.001
MMSE	3.25 (3.24)	−2 (2.61)	<0.001
Reasoning and cognitive level			
Colored progressive matrices	3.81 (6.72)	−2.36 (1.91)	0.004
Memory			
Digit span	−0.31 (0.95)	−0.27 (0.47)	ns
Corsi's test	−0.06 (0.85)	−0.09 (0.3)	ns
Serial repetition of two-syllabic words	0.19 (0.54)	0 (0)	ns
Rey's 15 words-immediate recall	0.13 (5.78)	−3.91 (2.91)	0.016
Rey's 15 words-delayed recall	0.31 (2.6)	−0.36 (0.92)	ns
Rey's complex figure-memory reproduction	1.22 (6.40)	−0.55 (1.97)	ns
Enhanced cued recall	1.00 (1.79)	−1.00 (1.1)	<0.001
Selective attention			
Digit cancellation test	3.93 (8.46)	−2.18 (3.76)	0.008
Praxis			
Imitating gestures test	8.17 (8.01)	−5.59 (3.85)	<0.001
Rey's complex figure-copy	5.11 (6.43)	−1.91 (3.14)	0.005
Frontal functions			
Frontal assessment battery	1.20 (2.70)	−0.91 (1.04)	0.015
Language			
Aachener aphasia test (AAT)—Token test	2.38 (2.96)	−1.64 (2.54)	0.001
AAT—Repetition	1.75 (2.11)	−1.18 (0.98)	<0.001
AAT—Written language	1.56 (3.14)	−0.64 (0.81)	0.014
AAT—Naming	3.88 (5.67)	−1.09 (0.70)	0.002
AAT—Comprehension	2.06 (6.88)	−0.73 (2.53)	ns

improvements in these domains, it could be effective in slowing down their worsening.

Regarding language abilities, comprehension and repetition appeared to have improved in the whole sample, but effect sizes were small; this result in persons with M-NCD is very important, given the relevant role of language in communication and in mediating interpersonal relationships. The g-ICA, indeed, in addition to specific language tasks, includes a massive and continuous exposure to verbal language, since it is the principal vehicle of relationships between the patients and between patients and the mediator. To date, there is no study in the literature showing specific benefits of cognitive interventions on verbal language. Also in this case, the comparison with the CG group was able to disclose a slowing of the expected worsening of these functions.

Regarding m-NCD, to the best of our knowledge, our study is the only one in which an integrated cognitive approach has been applied. The review by Wang et al. (2014) has confirmed that cognition–based intervention (namely CT, CS, or memory training) can be effective on global cognitive functioning and less evidently, executive functions and delayed memory in patients with MCI; we also found improved global cognitive function and reasoning abilities (CPM scores). MMSE did not change but this battery is probably not appropriate for detecting a mild cognitive decline; in fact, all the patients in this group showed scores higher than 24 at the pre-treatment assessment.

Also in m-NCD, memory domains, especially verbal memory, were very little modified and some benefits were observed only in verbal span (serial repetition of two-syllable words) and delayed visual-spatial memory. In summary, the benefits obtained from g-ICA treatment on global cognitive and frontal functions in individuals with m-NCD confirm those reported earlier in the literature; however, we detected additional benefits on praxis ability, attention and verbal language.

This study has limitations and strengths. One limitation is the absence of a CG for m-NCD patients. A second limitation is the relatively small sample size of our groups, already cited above. Another limitation of this study is that a specific relation between one strategy and its effects cannot be established with certainty because the g-ICA is a package of combined strategies; a cross-over design (treating EG patients with all of the three techniques) would have been appropriate and would have probably provided more detailed data, but it was not possible to implement it because of a series of practical and regulatory limitations that do not allow us to follow patients intensively for a period of time long enough. Another important limitation of this program is the absence of labs specifically equipped for daily living activities, which directly address one's own self-efficacy perception and therefore are fundamental, especially for persons with M-NCD. g-ICA includes procedures aimed to facilitate not only success in cognitive tasks, but also the general well-being of patients, but in this first study, which had the main objective to evaluate the cognitive effects of treatment, no measures of self-esteem, quality of life and self-awareness were used. Finally, this study had a baseline-treatment design that cannot allow strong conclusions on the direct cause of the effects detected, because of the impossibility to exclude competing hypotheses. However, our results are promising and indicate the need to carry out longer follow-up protocols in which an adequate CG can be included.

Despite the limitations, mediation pedagogy and the errorless learning can be considered to be important strengths of this study because they facilitate enhancement of motivation and removal of personal psychological barriers to cognitive treatment. Moreover, the rich neuropsychological battery has enabled the assessment of all the main cognitive functions, offering the opportunity to add useful information to the data already present in the literature. Since g-ICA is an intensive treatment, it allows patients to activate themselves cognitively for several hours, 5 days a week; on the contrary, previous studies in the literature usually describe treatments lasting for 45–50 min, delivered 4 days a week at most (Spector et al., 2003; Cipriani et al., 2006; Raggi et al., 2007; Talassi et al., 2007; Yamagami et al., 2012). The intensity of such a treatment was, most likely, another determining factor for the positive results obtained. The g-ICA turned out to be effective and well accepted by patients younger than 70–80 years, whereas studies in the literature have often reported results in older patients (Spector et al., 2003; Cipriani et al., 2006; Yamagami et al., 2012; Aguirre et al., 2013). Our treatment can be easily implemented in a hospital setting, it is cost-effective and represents an enrichment of the routine rehabilitation programs, as defined by the local regulations (Italian Government Essential Assistance Levels).

AUTHOR CONTRIBUTIONS

SP conceived the study. SP, DT, SM and RF contributed to the study design. SM, GP and CB participated in the diagnostic process and recruited the patients. DT, SM, FR and VC performed testing and data collection. DT and SM delivered the cognitive activation sessions. SP, AR and RF analyzed and interpreted the data. SP wrote the first version of the article. AR and RF provided critical revisions of the manuscript. All the authors read and approved the final version of the article.

ACKNOWLEDGMENTS

This research was supported by the Italian Ministry of Health (“Ricerca Corrente”). We are grateful to Dr. Rosi Di Giorgio for her contribution to the final version of this article.

REFERENCES

Aguirre, E., Hoare, Z., Streater, A., Spector, A., Woods, B., Hoe1, J., et al. (2013). Cognitive stimulation therapy (CST) for people with dementia—who benefits most? *Int. J. Geriatr. Psychiatry* 28, 284–290. doi: 10.1002/gps.3823

Alves, J., Magalhães, R., Machado, Á., Gonçalves, Ó. F., Sampaio, A., and Petrosyan, A. (2013). Non-pharmacological cognitive intervention for aging and dementia: current perspectives. *World J. Clin. Cases* 1, 233–241. doi: 10.12998/wjcc.v1.i8.233

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders.* 5th Edn. Washington: American Psychiatric Association.

Avila, R., Bottino, C. M. C., Carvalho, I. A. M., Santos, C. B., Seral, C., and Miotto, E. C. (2004). Neuropsychological rehabilitation of memory deficits and activities of daily living in patients with Alzheimer's disease: a pilot study. *Braz. J. Med. Biol. Res.* 37, 1721–1729. doi: 10.1590/s0100-879x2004001100018

Basso, A., Capitani, E., and Laiacona, M. (1987). Raven's colored progressive matrices: normative values on 305 adult normal controls. *Funct. Neurol.* 2, 189–194.

Bentwich, J., Dobronevsky, E., Aichenbaum, S., Shorer, R., Peretz, R., Khaigrekht, M., et al. (2011). Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. *J. Neural Transm. (Vienna)* 118, 463–471. doi: 10.1007/s00702-010-0578-1

Bianchi, A., and Dai Prà, M. (2008). Twenty years after Spinnler and Tognoni: new instruments in the Italian neuropsychologist's toolbox. *Neurol. Sci.* 29, 209–217. doi: 10.1007/s10072-008-0970-x

Bossen, A. L., Specht, J. K. P., and McKenzie, S. E. (2009). Needs of people with early-stage Alzheimer's disease: reviewing the evidence. *J. Gerontol. Nurs.* 35, 8–15. doi: 10.3928/00989134-20090301-01

Brazzelli, M., Capitani, E., Della Sala, S., Spinnler, H., and Zuffi, M. (1994). A neuropsychological instrument adding to the description of patients with suspected cortical dementia: the Milan overall dementia assessment. *J. Neurol. Neurosurg. Psychiatry* 57, 1510–1517. doi: 10.1136/jnnp.57.12.1510

Buschert, V., Bokde, A. L., and Hampel, H. (2010). Cognitive intervention in Alzheimer disease. *Nat. Rev. Neurol.* 6, 508–517. doi: 10.1038/nrneurol.2010.113

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., and Venneri, A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurol. Sci.* 22, 443–447. doi: 10.1007/s100720200003

Carlesimo, G. A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., et al. (2002). Standardizzazione di due test di memoria per uso clinico: breve racconto e figura di Rey. *Nuova Rivista Neurologia* 12, 1–13.

Carlesimo, G. A., Caltagirone, C., Gainotti, G., Fadda, L., Gallasi, R., Lorusso, S., et al. (1996). The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *Eur. Neurol.* 36, 378–384. doi: 10.1159/000117297

Celentano, K., Napoletano, A. E., and Lepore, M. (2002). “La riabilitazione della memoria semantica,” in *Amnesie e Disturbi Della Cognizione Spaziale*, eds D. Grossi and M. Lepore (Milano: Franco Angeli), 73–86.

Choi, J., and Twamley, E. W. (2013). Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol. Rev.* 23, 48–62. doi: 10.1007/s11065-013-9227-4

Cipriani, G., Bianchetti, A., and Trabucchi, M. (2006). Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment. *Arch. Gerontol. Geriatr.* 43, 327–335. doi: 10.1016/j.archger.2005.12.003

Clare, L., and Woods, R. T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. *Neuropsychol. Rehabil.* 14, 385–401. doi: 10.1080/09602010443000074

Cooper, J. O., Heron, T. E., and Heward, W. L. (2007). *Applied Behavior Analysis.* 2nd Edn. Upper Saddle River: Pearson Prentice Hall.

De Renzi, E., Motti, F., and Nichelli, P. (1980). Imitating gestures: a quantitative approach to ideomotor apraxia. *Arch. Neurol.* 37, 6–10. doi: 10.1001/archneur.1980.00500500036003

Dubois, B., Slachevsky, A., Litvan, I., and Pillon, B. (2000). The FAB: a frontal assessment battery at bedside. *Neurology* 55, 1621–1626. doi: 10.1212/wnl.55.11.1621

Feuerstein, R. (1999). *Mediated Learning Experience (MLE): Theoretical, Psychosocial and Learning Implications.* Tel Aviv: Freund Publishing House.

Florenzano, F. (1988). *La Reality Orientation in Psicogeriatria.* Roma: Primerano.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Grober, E., Buschke, H., Crystal, H., Bang, S., and Dresner, R. (1988). Screening for dementia by memory testing. *Neurology* 38, 900–903. doi: 10.1212/wnl.38.6.900

Hildreth, K. L., and Church, S. (2015). Evaluation and management of the elderly patient presenting with cognitive complaints. *Med. Clin. North Am.* 99, 311–335. doi: 10.1016/j.mcna.2014.11.006

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., and Martin, R. L. (1982). A new clinical scale for the staging of dementia. *Br. J. Psychiatry* 140, 566–572. doi: 10.1192/bjp.140.6.566

Jedrziewski, M. K., Ewbank, D. C., Wang, H., and Trojanowski, J. Q. (2014). The impact of exercise, cognitive activities and socialization on cognitive function: results from the national long-term care survey. *Am. J. Alzheimers Dis. Other Demen.* 29, 372–378. doi: 10.1177/1533317513518646

Katz, S., Downs, T. D., Cash, H. R., and Grotz, R. C. (1970). Progress in development of the index of ADL. *Gerontologist* 10, 20–30. doi: 10.1093/geront/10.1_part_1.20

Knapp, M., Thorgrimsen, L., Patel, A., Spector, A., Hallam, A., Woods, B., et al. (2006). Cognitive stimulation therapy for people with dementia: cost-effectiveness analysis. *Br. J. Psychiatry* 188, 574–580. doi: 10.1192/bjp.bp.105.010561

Langa, K. M., and Levine, D. A. (2014). The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA* 312, 2551–2561. doi: 10.1001/jama.2014.13806

Law, L. L., Barnett, F., Yau, M. K., and Gray, M. A. (2014). Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: a systematic review. *Ageing Res. Rev.* 15, 61–75. doi: 10.1016/j.arr.2014.02.008

Lawton, M. P., and Brody, E. (1969). Assessment of older people: self-monitoring and instrumental activities of daily living. *Gerontologist* 9, 179–186. doi: 10.1093/geront/9.3_part_1.179

Loewenstein, D. A., Acevedo, A., Czaja, S. J., and Duara, R. (2004). Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. *Am. J. Geriatr. Psychiatry* 12, 395–402. doi: 10.1097/00019442-200407000-00007

Luzzatti, C., Willmes, K., and De Blaser, R. (1996). *AAT–Aachener Aphasie Test. Italian Version.* Firenze: Giunti OS Organizzazioni Speciali.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

National Institute for Health and Clinical Excellence. (2007). *Dementia: Supporting People with Dementia and their Carers in Health and Social Care. NICE Clinical Guideline 42.* London: National Institute for Health and Clinical Excellence.

Olazarán, J., Muniz, R., Reisberg, B., Peña-Casanova, J., del Ser, T., Cruz-Jentoft, A. J., et al. (2004). Benefits of cognitive motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology* 63, 2348–2353. doi: 10.1212/01.wnl.0000147478.03911.28

Olazarán, J., Reisberg, B., Clare, L., Cruz, I., Peña-Casanova, J., Del Ser, T., et al. (2010). Non-pharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement. Geriatr. Cogn. Disord.* 30, 161–178. doi: 10.1159/000316119

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., and Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital. J. Neurol. Sci.* 8, 539–548. doi: 10.1007/bf02333660

Raggi, A., Iannaccone, S., Marcone, A., Ginex, V., Ortelli, P., Nonis, A., et al. (2007). The effects of a comprehensive rehabilitation program of Alzheimer's disease in a hospital setting. *Behav. Neurol.* 18, 1–6. doi: 10.1155/2007/782959

Requena, C., Maestú, F., Campo, P., Fernández, A., and Ortiz, T. (2006). Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. *Dement. Geriatr. Cogn. Disord.* 22, 339–345. doi: 10.1159/000095600

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., et al. (2014). Classifying neurocognitive disorders: the DSM-5 approach. *Nat. Rev. Neurol.* 10, 634–642. doi: 10.1038/nrneurol.2014.181

Schwartz, L. (1990). *What Would You Do?* Huntington Beach: Creative Teaching Press.

Schwartz, L. (1993). *What Do You Think?* Huntington Beach: Creative Teaching Press.

Simon, S. S., Yokomizo, J. E., and Bottino, C. M. (2012). Cognitive intervention in amnestic mild cognitive impairment: a systematic review. *Neurosci. Biobehav. Rev.* 36, 1163–1178. doi: 10.1016/j.neubiorev.2012.01.007

Sitzer, D. I., Twamley, E. W., and Jeste, D. V. (2006). Cognitive training in Alzheimer's disease: a meta-analysis of the literature. *Acta Psychiatr. Scand.* 114, 75–90. doi: 10.1111/j.1600-0447.2006.00789.x

Spector, A., Thorgrimsen, L., Woods, B., and Orrell, M. (2006). *Making a Difference: An Evidence Based Group Programme to Offer Cognitive Stimulation Therapy (CST) to People with Dementia: Manual for Group Leaders.* UK: Hawker Publications.

Spector, A., Thorgrimsen, L., Woods, B., Royan, L., Davies, S., Butterworth, M., et al. (2003). Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br. J. Psychiatry* 183, 248–254. doi: 10.1192/bjp.183.3.248

Spinnler, H., and Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 8, 1–120.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460. doi: 10.1017/s1355617702813248

Stern, Y. (2013). Cognitive reserve: implication for assessment and intervention. *Folia Phoniatr. Logop.* 65, 49–54. doi: 10.1159/000353443

Talassi, E., Guerreschi, M., Feriani, M., Fedi, V., Bianchetti, A., and Trabucchi, M. (2007). Effectiveness of a cognitive rehabilitation program in mild dementia (MD) and mild cognitive impairment (MCI): a case control study. *Arch. Gerontol. Geriatr.* 44, 391–399. doi: 10.1016/j.archger.2007.01.055

Taulbee, L. R., and Folsom, J. C. (1966). Reality orientation for geriatric patients. *Hosp. Community Psychiatry* 17, 133–135. doi: 10.1176/ps.17.5.133

Traykov, L., Rigaud, A. S., Cesaro, P., and Boller, F. (2007). Neuropsychological impairment in the early Alzheimer's disease. *Encephale* 33, 310–316. doi: 10.1016/S0013-7006(07)92044-8

Wang, C., Yu, J. T., Wang, H. F., Tan, C. C., Meng, X. F., and Tan, L. (2014). Non-pharmacological interventions for patients with mild cognitive impairment: a meta-analysis of randomized controlled trials of cognition-based and exercise interventions. *J. Alzheimers Dis.* 42, 663–678. doi: 10.3233/JAD-140660

Woods, B., Aguirre, E., Spector, A. E., and Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst. Rev.* 2:CD005562. doi: 10.1002/14651858.cd005562.pub2

Yamagami, T., Takayama, Y., Maki, Y., and Yamaguchi, H. (2012). A randomized controlled trial of brain-activating rehabilitation for elderly participants with dementia in residential care homes. *Dement. Geriatr. Cogn. Disord. Extra* 2, 372–380. doi: 10.1159/000342614

Yamaguchi, H., Maki, Y., and Yamagami, T. (2010). Overview of non-pharmacological intervention for dementia and principles of brain-activating rehabilitation. *Psychogeriatrics* 10, 206–213. doi: 10.1111/j.1479-8301.2010.00323.x

Yuill, N., and Hollis, V. (2011). A systematic review of cognitive stimulation therapy for older adults with mild to moderate dementia: an occupational therapy perspective. *Occup. Ther. Int.* 18, 163–186. doi: 10.1002/oti.315

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

REVIEW
published: 27 October 2015
doi: 10.3389/fnbeh.2015.00281

Active training for amblyopia in adult rodents

Alessandro Sale[1] and Nicoletta Berardi[1,2]**

[1] Neuroscience Institute, National Research Council, Pisa, Italy, [2] Department of Neuroscience, Psychology, Drug Research and Child Health NEUROFARBA, University of Florence, Florence, Italy

Amblyopia is the most diffused form of visual function impairment affecting one eye, with a prevalence of 1–5% in the total world population. Amblyopia is usually caused by an early functional imbalance between the two eyes, deriving from anisometropia, strabismus, or congenital cataract, leading to severe deficits in visual acuity, contrast sensitivity and stereopsis. While amblyopia can be efficiently treated in children, it becomes irreversible in adults, as a result of a dramatic decline in visual cortex plasticity which occurs at the end of the critical period (CP) in the primary visual cortex. Notwithstanding this widely accepted dogma, recent evidence in animal models and in human patients have started to challenge this view, revealing a previously unsuspected possibility to enhance plasticity in the adult visual system and to achieve substantial visual function recovery. Among the new proposed intervention strategies, non invasive procedures based on environmental enrichment, physical exercise or visual perceptual learning (vPL) appear particularly promising in terms of future applicability in the clinical setting. In this survey, we will review recent literature concerning the application of these behavioral intervention strategies to the treatment of amblyopia, with a focus on possible underlying molecular and cellular mechanisms.

Keywords: amblyopia, environmental enrichment, physical exercise, visual perceptual learning, GABAergic inhibition

Edited by:
Benedetto Sacchetti, University of Turin, Italy

Reviewed by:
Marco Sassoè-pognetto, University of Turin, Italy
Frauke Nees, Central Institute of Mental Health, Germany

****Correspondence:***
Alessandro Sale
sale@in.cnr.it;
Nicoletta Berardi
berardi@in.cnr.it

Received: *07 July 2015*
Accepted: *06 October 2015*
Published: *27 October 2015*

Citation:
Sale A and Berardi N (2015) Active training for amblyopia in adult rodents. Front. Behav. Neurosci. 9:281. doi: 10.3389/fnbeh.2015.00281

INTRODUCTION

During development, brain plasticity is high and neurons adapt promptly in response to environmental stimuli, but with the passage from youth to adulthood neural circuits become much less plastic. The decay in plasticity levels strongly prevents, in the mature brain, the possibility for functional recovery from developmental disorders. This condition is epitomized by amblyopia, a visual disorder affecting thousands of people; if not precociously recognized and treated, amblyopia has proven to be substantially insensitive to treatment after the age of 7–8 years. However, recent research has demonstrated the previously unsuspected possibility to elicit robust plasticity in the adult visual system and to promote recovery of visual abilities even in adult amblyopic subjects.

In the present survey, we shall review the recent literature on this hot topic, focusing on two non invasive treatment strategies which hold promise for successful clinical application in amblyopes: physical exercise and visual perceptual learning (vPL). In the first section, we introduce the relation between amblyopia and critical period (CP) for experience-dependent plasticity in the visual cortex, both in humans and in animal models. In the second section, we review the experimental strategies showing the possibility for recovery from amblyopia, starting with the description of the striking results obtained with pharmacological approaches acting on visual cortical plasticity and following with the discussion of the effects elicited by environmental enrichment procedures based on an increase in sensory-motor stimulation. In the third section, we shall focus on recent data showing that physical exercise and vPL are behavioral interventions particularly suited for cortical plasticity enhancement and recovery from amblyopia. In the last section, we discuss possible cellular and molecular mechanisms underlying the beneficial effects of physical exercise and vPL on visual cortical plasticity. Finally, we underline possible open questions and future research directions.

AMBLYOPIA AND ITS MODELING IN LABORATORY ANIMALS

Amblyopia (lazy eye), is a major developmental visual disorder that occurs in 1–5% of the world population and is typically caused by an early abnormal visual experience which occurs during a well defined CP, which is around 6–8 years of age in children. Typical causes of amblyopia are strabismus, image degradation due to refractive errors, or congenital cataract (Holmes and Clarke, 2006). The most common form of the disorder, unilateral amblyopia, results in a marked visual acuity impairment in the affected eye, together with reduced stereopsis, and low contrast and motion sensitivity. The physiology of the retina is generally spared in amblyopia (e.g., Sherman and Stone, 1973; Kratz et al., 1979; Baro et al., 1990), while the lateral geniculate nucleus of the thalamus (LGN) can appear atrophic (Wiesel and Hubel, 1963). There is large consensus, however, that amblyopia is prevalently caused by neural dysfunctions occurring in the primary visual cortex (V1; see Hess, 2001; Barrett et al., 2004).

Most important, recovery of normal visual functions is almost impossible after CP end, i.e., after 8 years of age in children. Thus, the CP for the appearance of amblyopia is paralleled by a sensitive period for the success of therapeutic strategies (see Lewis and Maurer, 2009).

Use of animal models of amblyopia has largely increased our knowledge on the neural mechanisms underlying this pathology. In kittens and rodents, the most widely diffused model of amblyopia is obtained by strongly reducing visual input to one eye by lid suture, a procedure usually referred to as monocular deprivation (MD). MD performed during the CP decreases the presence of binocular neurons in V1, reduces the number of neurons responding more vigorously to the deprived than to the non deprived eye, resulting in an increase of neurons dominated by the open eye; behaviorally, a loss of binocular vision and a strong reduction of visual acuity and contrast sensitivity for the deprived eye is observed (e.g., Wiesel and Hubel, 1963; Hubel and Wiesel, 1970; Olson and Freeman, 1975; Movshon and Dürsteler, 1977; Pizzorusso et al., 2006; Sale et al., 2007).

As found in humans, the effects of MD can be at least partially reversed if normal visual input is reestablished during the CP (e.g., Blakemore et al., 1981; Antonini and Stryker, 1998; Pizzorusso et al., 2006; Sale et al., 2007). The basic strategy for treating amblyopia during CP is to remove the defects preventing a clear retinal image and to promote strengthening of neural connections coming from the lazy eye. So called "passive methods" such as refractive correction, alone or in combination with fellow eye patching or atropine penalization, are widely employed, with a percentage of success correlating with the total number of treatment hours (Foley-Nolan et al., 1997; Simons et al., 1997; Pediatric Eye Disease Investigator Group, 2002; Wu and Hunter, 2006).

These strategies do not lead to vision recovery if applied well after CP end and no successful therapy has been available for adult patients, so that amblyopia in adult subjects has long been considered an irreversible condition; lack of recovery was attributed to the dramatic decline in visual cortex plasticity that accompanies the transition from youth to adulthood and prevents visual cortical connections from remodeling in favor of the deprived eye input, following removal of its visual defects (e.g., Blakemore et al., 1981; Antonini and Stryker, 1998; Pizzorusso et al., 2006; Sale et al., 2007).

CHALLENGING THE DOGMA OF IRREVERSIBILITY

If the lack of recovery from amblyopia in adult subjects is due to the low levels of plasticity of adult V1, enhancing V1 plasticity might allow the deprived eye input to regain access to visual cortical neurons, promoting recovery from amblyopia. Following this hypothesis, a new era of exciting experimental studies has recently started, leading to the demonstration and now widely accepted notion that a high degree of residual cortical plasticity can be unmasked in the adult brain (see, for instance, the review by Bavelier et al., 2010).

Pharmacological Studies

The first studies have exploited pharmacological treatments to either target factors that brake adult plasticity and/or to enhance levels of endogenous permissive molecules.

The excitatory/inhibitory (E/I) balance in V1 rapidly emerged as a crucial factor in controlling the opening and time course of CP plasticity (Hensch, 2005; Sugiyama et al., 2008); in particular, direct pharmacologically reduction of GABAergic transmission in the adult visual cortex has proven to be a suitable strategy for the restoration of plasticity processes (Hensch, 2005; Harauzov et al., 2010; Baroncelli et al., 2011). Interestingly, also transplantation of embryonic inhibitory neuronal precursors into the visual cortex of post-CP animals can induce a second window of plasticity after the end of the natural CP (Southwell et al., 2010). Whether these treatments are also capable to promote recovery from amblyopia is still unknown. A change in V1 E/I balance has also been achieved indirectly, pharmacologically targeting neuromodulators, such as serotonin, norepinephrine, and acetylcholine, which are known to be strongly involved in visual plasticity (Kasamatsu and Pettigrew, 1976; Bear and Singer, 1986; Kilgard and Merzenich, 1998; Bao et al., 2001; Goard and Dan, 2009) and which proved to impinge on E/I balance and to promote recovery from amblyopia (e.g., Maya Vetencourt et al., 2008; Bavelier et al., 2010; Morishita et al., 2010; Sale et al., 2014, for review) As an example, chronic delivery in the drinking water of the selective serotonine-reuptake inhibitor (SSRI) fluoxetine caused a marked decrease of GABAergic inhibition levels in V1 and this decrease was crucial for fluoxetine to enhance V1 experience-dependent plasticity and to promote visual function recovery in adult amblyopic rats following reopening of the initially deprived eye and closure of the normal eye (Maya Vetencourt et al., 2008).

Other successful pharmacological studies have targeted the adult brain extracellular milieu, making it more permissive for experience-dependent plasticity. Chondroitinase ABC, an enzyme responsible for the degradation of chondroitin sulfate proteoglycans (CSPGs) in the extracellular matrix, enhances V1 experience-dependent plasticity and induces full recovery from amblyopia in adult rats (Pizzorusso et al., 2002, 2006). Interestingly, some of the effects elicited by Chondroitinase ABC could be mediated by modifications of intracortical inhibitory circuits occurring after degradation of extracellular matrix perineuronal nets (PNNs; Hensch, 2005). An involvement of intracortical inhibitory circuits and of CSPGs has also been shown for the effects on V1 plasticity of the orthodenticle homeobox 2 (Otx2) homeoprotein, which transfers to parvalbumin-positive GABAergic interneurons in the developing mouse visual cortex, acting as a direct trigger both for the opening and closure of the CP (Sugiyama et al., 2008). CSPGs are necessary to capture endogenous Otx2 at the surface of parvalbumin interneurons, via the so called RK peptide (Beurdeley et al., 2012). Reducing CSPGs by means of chondroitinase ABC leads to a reduction in the amount of endogenous Otx2 bound to parvalbumin cells, and so does infusion of RK peptide which competes with the endogenous one; both treatments lead to functional recovery in adult amblyopic mice (Beurdeley et al., 2012).

Finally, a very attractive and relatively new kind of pharmacological substances acts at the level of epigenetic modifications of the brain chromatin status (Zhang and Meaney, 2010). The closure of the CP in the mouse visual cortex has been linked to downregulation of histone H3 and H4 acetylation (Putignano et al., 2007); accordingly, infusion of histone deacetylase inhibitors enhances plasticity in adult V1, leading to functional recovery in amblyopic rats past the end of the CP (Silingardi et al., 2010).

Non Pharmacological Studies

Results more suitable for clinical application have been obtained by means of non invasive treatments aimed at inducing an endogenous recapitulation of the brain states that enhance V1 plasticity. Dark exposure initiated in adulthood reactivates synaptic plasticity in the visual cortex, induces recovery of dendritic spine density of neurons and promotes vision rescue in long-term MD rats (He et al., 2007; Montey and Quinlan, 2011). Thus, these results raise the provocative concept that darkness might be a cure for vision loss in amblyopia, a fascinating approach which however, appears quite limited in terms of human application.

A more promising approach is based on somewhat opposite strategies leading to the optimization and enhancement of sensory stimuli. The progenitor of this kind of treatments is environmental enrichment (EE; van Praag et al., 2000; Sale et al., 2014), whereby laboratory rodents are reared in large social groups in wide and attractive cages where a variety of toys are available and changed frequently to stimulate motor activity, novelty and curiosity as determinants of exploratory behavior. Adult amblyopic rats reared under EE conditions display a full rescue of their visual functions (Sale et al., 2007): moreover, EE is also able to reopen the CP for V1 plasticity in response to MD, even in aged rats (Baroncelli et al., 2010; Scali et al., 2012). Importantly, exposure to EE does also result in a marked reinstatement of visual depth-perception abilities of adult amblyopic animals, as tested with the visual cliff task (Baroncelli et al., 2013).

Mediators of EE effects include E/I balance and neuromodulators as well as other well known determinant of CP plasticity such as brain-derived neurotrophic factor (BDNF) and CSPGs (see Sale et al., 2014). Neuromodulators were known to respond to EE since the very first studies in the 60s which reported an increase in acetylcholinesterase activity, with subsequent work confirming and extending this initial observation to the other neuromodulator systems, like the serotonin and noradrenaline systems (van Praag et al., 2000). In the visual cortex, an enhanced serotonin expression has been shown to be critical for plasticity enhancement in adult enriched rats (Baroncelli et al., 2010), a result linking the impact of EE on visual cortical plasticity to the previously discussed importance of neuromodulating systems for CP reopening in the mature visual cortex. Moreover, recovery of plasticity in enriched amblyopic animals is associated with reduction of GABA release in the visual cortex, as assessed by brain microdialysis, enhancement of BDNF expression and with decrease of CSPG condensation in perineuronal nets in the visual cortex (Sale et al., 2007).

ACTIVE TRAINING FOR AMBLYOPIA

One step up toward the application of the EE paradigm to human subjects is to study the role of selected EE components in the reopening of visual cortex plasticity. In a first attempt to evaluate the efficacy of motor activity, social stimulation, or enhanced visual stimulation in promoting amblyopia recovery in the rat model, we reported a full recovery of ocular dominance and visual acuity both in animals experiencing high levels of voluntary motor activity in a running wheel and in rats exposed to a protocol of passive visual enrichment consisting on a rotating visual drum (Baroncelli et al., 2012), but not in animals subjected only to social enrichment. In agreement with previous results, those EE components found to be effective in triggering recovery from amblyopia were associated with a decreased GABA release in the visual cortex, without any change in the release of glutamate, thus resulting in a damped intracortical inhibition/excitation ratio (Baroncelli et al., 2012).

Among the various EE components, physical activity emerges as one of the most crucial, with numerous studies reporting its striking capability to mimic the more complex EE approach in producing a number of different beneficial effects (see Sale et al., 2014 for a recent survey). In a series of elegant works, Michael Stryker and colleagues have not only shown that locomotion powerfully increases visual responsiveness in the primary visual cortex (Niell and Stryker, 2010), but have also demonstrated that the enhancement of visual responses induced by locomotion is sufficient to promote recovery of visual function (Kaneko and Stryker, 2014) and provided evidence on the possible neural circuit underlying these effects (Fu et al., 2014, 2015; Lee et al., 2014). Niell and Stryker (2010) studied the response properties of neurons in primary visual cortex of awake mice while animals run on a freely rotating spherical treadmill with their heads fixed. They found that locomotor activity was associated with a dramatic increase in visual responsiveness in essentially all broad-spiking (presumed excitatory) cells without any concurrent changes in spontaneous firing rate or tuning properties; thus, increase in visually-evoked firing rate was not obtained at the expense of stimulus selectivity. The response magnitude of neurons in the visual thalamus was not affected by locomotion, indicating that the modulation of visual responses by locomotion is a cortical effect. Locomotion was also correlated with a decrease in low frequency power and an increase in the amplitude of the high-frequency gamma peak in the local EEG, suggesting a transition to a different cortical state during locomotion. Because the mice were not actively engaged in a perceptual task, and the increase in response was seen across the visual field, it seems likely that it reflects a general activation associated with locomotion, akin to arousal, rather than a mechanism of selective attention. The dependence on behavioral state was cell-type specific, in that a subset of the narrow-spiking cells (presumed inhibitory interneurons), which had little activity when the animal was stationary, began firing at high spontaneous rates during movement but then showed a suppressive response to visual stimuli.

It was evident that cortical activation associated with locomotion acted as a gain modulator, increasing responsiveness without changing selectivity. Thus, the increase in amplitude of visual responses during locomotion might provide a stronger drive for experience dependent visual cortical plasticity, increasing the capacity for recovery from early visual deprivation in the visual cortex of adult animals. In line with what we found in animals free to run on a running wheel in a condition of reversed suture (Baroncelli et al., 2012), visual responses to stimuli presented to the initially deprived eye during locomotion on a spherical treadmill (head fixed) increased significantly, reaching almost normal level after 7 days, and ocular dominance of visual cortical neurons was recovered (Kaneko and Stryker, 2014). The interesting thing is that increased responsiveness to deprived eye input and ocular dominance (OD) recovery was seen also under binocular vision, not only after reverse suture (reopening of the formerly deprived eye and closure of the non deprived eye). The recovery of response to stimuli presented to the formerly deprived eye was specific for the particular visual stimuli presented during locomotion, suggesting that recovery is facilitated only in the neural circuits that are activated during running.

Thus, it seems that enriching the environment in terms of voluntary motor activity and/or visual stimulation is a potentially useful strategy to reopen visual cortex plasticity and favor recovery of function in adult amblyopic subjects. How to apply the animal EE paradigm to humans is still debated. One approach very akin to EE is represented by active videogames, which combine various EE components such as visual attention and enhanced sensory stimulation (see Green and Bavelier, 2012). The videogame approach has been now tested in adult subjects with amblyopia, with encouraging results (Li et al., 2011).

Another promising strategy for amblyopia recovery which can be considered conceptually similar to EE is vPL, defined as the performance improvement, following practice, in visual tasks of different nature and complexity (see Bonaccorsi et al., 2014 for a recent review). A key property of vPL is its high specificity for the main stimulus attributes (e.g., stimulus orientation and location in the visual field), with the achieved performance typically returning to pre-learning baseline levels when test trials move to even slightly changed stimuli (McKee and Westheimer, 1978; Fiorentini and Berardi, 1980, 1981; Ball and Sekuler, 1982, 1987; Sale et al., 2011; see also Bonaccorsi et al., 2014).

vPL as a treatment for amblyopia has been first introduced in human patients, and it is currently considered one of the more promising strategies to favor recovery of visual functions in adult amblyopic subjects. The tasks used to elicit vPL are various, with examples of letter identification or longitudinal Vernier acuity and contrast sensitivity assessment (e.g., Levi and Polat, 1996; Levi et al., 1997; Polat et al., 2004; Li and Levi, 2004; Levi, 2005; Li et al., 2005, 2007; Chung et al., 2006, 2008; Zhou et al., 2006; Huang et al., 2008; Levi and Li, 2009). Significant improvements have been shown to be at reach in multiple domains, such as visual acuity, contrast sensitivity, and stereoacuity, with the learned improvements being frequently able to generalize to novel tasks (see Astle et al., 2011).

One consideration to make before moving to discuss the possible mechanisms of action of vPL and physical exercise in enhancing visual plasticity and promote recovery from amblyopia is that despite the interest for application of physical exercise and perceptual learning in the treatment of visual deficits in adult amblyopic subjects, to date there has been no attempt to understand whether the same procedures could also accelerate visual function recovery in developing subjects (both in humans and animal models). Such information might be instrumental for designing new therapeutic approaches aimed at speeding up the process of visual function recovery in amblyopic children.

NEURAL CHANGES UNDERLYING THE BENEFICIAL EFFECTS OF PHYSICAL EXERCISE AND VISUAL PERCEPTUAL LEARNING ON VISUAL PLASTICITY AND RECOVERY FROM AMBLYOPIA

Physical Exercise

In the Niell and Stryker (2010) article, the authors made two predictions. First, if the narrow-spiking units whose visual response was suppressed during locomotion did turn out to be inhibitory, they might play a crucial role in the cortical response to locomotor activation. Their increased firing rate during locomotion would increase overall inhibition, serving to keep spontaneous rates relatively constant; in the presence of a visual stimulus, the reduction in their firing would relieve this inhibition, allowing the high-amplitude responses observed during locomotion.

Second, they hypothesized a role for the neuromodulator acetylcholine (Ach). ACh has been demonstrated to play a role in cortical activation and attentional modulation in many systems (Hasselmo and Giocomo, 2006; Weinberger, 2007). The shift from low to high frequency in the local EEG spectrum is a characteristic of the actions of Ach and in particular of nucleus basalis stimulation (Buzsaki et al., 1988; Metherate et al., 1992; Rodriguez et al., 2004). Furthermore, cholinergic agonists have been shown to enhance visual responses in V1, without significant change in selectivity or spontaneous rate (Sillito and Kemp, 1983; Sato et al., 1987). In addition, nucleus basalis stimulation in the anesthetized rat has been shown to increase the reliability of visual responses to movies of natural scenes (Goard and Dan, 2009).

To dissect the circuits underlying locomotion effects on visual cortical responsiveness, Fu et al. (2014) took advantage of advances in mouse genetics and *in vivo* imaging technology to characterize the responses of different types of inhibitory neurons in mouse V1 in awake animals free to run on the spherical treadmill. In mice with Vasoactive Intestinal Peptide (VIP)-positive GABAergic neurons genetically labelled, the authors imaged the calcium responses of these VIP neurons in freely running head-fixed mice with or without visual stimulation. They found that the neural activity of VIP neurons, but not of non VIP neurons, is greatly elevated during locomotion even without visual stimulation. Visual stimulation, which drove the other cortical neurons, did not further increase the activation of VIP neurons by locomotion. A similar approach revealed that somatostatin (SST) neurons were inhibited by locomotion, consistent with a circuit in which VIP cells increase activity of neighboring excitatory cells by inhibiting their inhibitory input from SST cells. Activating VIP neurons in mouse V1 by means of optogenetic in stationary mice mimicked the effect of locomotion and increased the visual responses of visual cortical neurons, while focal damage to VIP neurons blocked the enhancement of cortical responses by locomotion.

The local blockade of nicotinic cholinergic input, but not of glutamatergic input, reduced the response of VIP neurons to locomotion by more than two thirds, and measurements *in vitro* disclosed powerful nicotinic cholinergic input to VIP neurons. Consistent with this result, upper layer VIP neurons in V1 turned out to receive direct input from the nucleus of the diagonal band of Broca (NDB), a cholinergic center in basal forebrain (Fu et al., 2014).

The cortical VIP-SOM circuit is also the mediator of locomotion induced enhancement of adult visual cortical plasticity (Fu et al., 2015). Genetically silencing VIP synaptic transmission in binocular zone of mouse V1 prevents locomotion from enhancing recovery of the amblyopic eye cortical responses. The involvement of VIP neurons in locomotion-induced enhancement of adult V1 plasticity has also been shown with a different approach, that is employing a brief MD in adult mice as a probe for OD plasticity. Between four to five days MD is insufficient to significantly shift OD in adult mice, due to the low OD plasticity, but they become effective if coupled with locomotion. Genetically silencing VIP neuron synaptic transmission in running mice makes MD ineffective in shifting OD of cortical neurons; optogenetic activation of VIP neurons in non running mice reproduced the plasticity-enhancement effects of locomotion. Silencing SST neurons turned out to be as effective as activating VIP neurons for enhancing adult OD plasticity in response to brief MD.

Altogether, these results are consistent with the idea that reduced inhibition is permissive for enhancing adult visual cortical plasticity (Harauzov et al., 2010; Sale et al., 2014) and reveal a disinhibitory circuit, VIP-SOM, that may underlie the reduction in GABA content and release in V1 found in EE or physical exercised mice in correlation with a strong enhancement of V1 plasticity and with recovery from amblyopia (Sale et al., 2007; Baroncelli et al., 2010, 2012).

The starting point of this cholinergic-VIP-SOM neuron mediated cortical response enhancement seems to be the mesencephalic locomotor region (MLR; Lee et al., 2014). MLR is the midbrain region the activation of which is sufficient to induce locomotion and is associated with the "ascending reticular activating system" described by Moruzzi and Magoun; electrical stimulation of this region can induce physiological correlates of alertness, such as desynchronization of low-frequency oscillations (<10 Hz) of the electroencephalogram (Moruzzi and Magoun, 1949).

Lee et al. (2014) found that optogenetic stimulation of MLR in awake, head-fixed mice induced both locomotion and increases in the gain of cortical responses in V1. Subthreshold optogenetic stimulation of the MLR was sufficient to increase the gain of visual responses and enhance gamma oscillations similar to those normally associated with locomotion even in the absence of overt movement. Furthermore, stimulation of axon terminals projecting from the MLR to cholinergic basal forebrain also reproduced this effect, suggesting that the MLR can influence cortical processing, potentially through projections directed toward the basal forebrain. These findings can be used to build a simple model in which the MLR initiates locomotion through descending pathways to the spinal cord while coordinating changes in brain state through its ascending projections.

Running and locomotion is associated not only with activation of cortical VIP neurons, but also with increases in multiple neuromodulators, including serotonin, which has been shown to be enhanced in V1 by EE (Baroncelli et al., 2010) and to promote adult V1 plasticity (Maya Vetencourt et al., 2008); interestingly, VIP neurons express the 5-HT3 serotonin receptor (Lee et al., 2014), suggesting that the VIP-SST disinhibitory circuit might be involved also in the effects of 5-HT on cortical plasticity. However, as suggested by Fu et al. (2015), enhancement of adult plasticity by locomotion is likely to be more complex than simply activating VIP-SST disinhibitory circuit.

Visual Perceptual Learning

vPL has been related to a number of different cellular mechanisms, including an increase in the number of neurons representing the learned stimulus (Recanzone et al., 1992, 1993) or, alternatively, more subtle functional changes at the levels of single neurons, both in terms of response strength and tuning (see Schummers et al., 2005). An obvious candidate mechanism underlying the cortical changes induced by vPL is synaptic plasticity. Gilbert and Li (2013) proposed that vPL is associated with long-term changes in either top-down circuits conveying information about attention and behavioral expectation, and in bottom-up circuits directly involved in experience-dependent changes. In agreement with this model, neurons in V1 are known to be capable of extensive integration well beyond the borders of their receptive fields, a property dependent of the existence of strong horizontal connections linking columns with similar orientation preference (Stettler et al., 2002; Stepanyants et al., 2009). While changes in favor of synaptic plasticity processes underlying perceptual learning has been recorded both in the primary motor cortex and in V1 in humans and non human primates (e.g., Rioult-Pedotti et al., 2000; Li et al., 2008; Yotsumoto et al., 2008), conclusive evidence has remained elusive.

The vPL approach in humans has informed and inspired increasing experimental work in simple animal models, mostly devoted to understand the mechanisms underlying the remarkable effects elicited by visual training. Frenkel et al. (2006) reported that, in the mouse, exposure to visual stimuli represented by gratings of a given orientation potentiates visual responses to the same orientation, an NMDA dependent experience-induced response enhancement called stimulus-selective response potentiation (SRP). We recently reported a more direct evidence for a synaptic plasticity engagement in vPL (Sale et al., 2011). To elicit vPL, we trained adult rats in a visual discrimination task in which they had to discriminate two visual gratings of very different spatial frequency; once the animals learned the task, the two stimuli were rendered progressively more similar to each other, providing a training process with increasing task difficulty. We observed a progressive improvement of discrimination ability with training, with performance reaching a steady plateau after few days. This kind of vPL turned out to be strictly selective for the orientation of the gratings employed during training, indicating that it requires activation of V1 circuits. A group of control rats learned the associative task in which they were required to discriminate two gratings of very different spatial frequency and then practiced with this easily discriminable pair of gratings for the same amount of days as vPL animals. When tested within 1 h from the last discrimination trial, long-term potentiation (LTP) elicited by theta burst stimulation applied to layer II-III of V1 slices appeared occluded in vPL animals compared to controls, both when testing its inducibility in vertical and horizontal connections. Moreover, the amplitudes of field potentials turned out to be increased in trained animals compared to controls, indicating that learning leads to a synaptic potentiation of V1 connections; no potentiation or LTP occlusion was found in control animals (Sale et al., 2011). These data provide a strong indication that the improvements displayed by vPL rats can be explained in terms of long-term increments of synaptic efficacy in V1 caused by learning, as already well known for different brain regions, such as hippocampus, amygdala and motor cortex (Rogan et al., 1997; Rioult-Pedotti et al., 1998; Whitlock et al., 2006).

The possibility to strengthen synaptic efficacy using vPL is attractive in terms of application to amblyopia therapy. Adult amblyopic rats trained in the same vPL task displayed robust recovery of visual acuity and ocular dominance (Baroncelli et al., 2012), an effect persisting for quite a long time (i.e., 14 days, corresponding to at least 20 months in the timescale of human life). In search for possible molecular candidates underlying the beneficial effects of vPL, we found that it resulted in a decrease of the inhibition-excitation balance in V1. Vision recovery was instead totally absent in those control groups in which the treatment did not induce LTP in V1, i.e., in rats that were trained only until the first step of the discrimination procedure between the test and the reference grating, without proceeding further with a progression of finer discrimination trials (Baroncelli et al., 2012). The control group performed an equal amount of physical activity in the maze with respect to the animals trained in the vPL task, ruling out the possibility that the physical exercise component intrinsic to the employed vPL procedure might contribute to visual function recovery. This conclusion could seem at odd with the striking capability of running (Baroncelli et al., 2012) to promote recovery of ocular dominance and visual acuity in amblyopic subjects. It has to be noted, however, that while, in the study by Baroncelli et al. (2012) running was a form of voluntary exercise, swimming activity in the water maze is necessarily imposed. A vast literature exists pointing out different effects elicited by voluntary vs. forced motor behavior on brain and behavior, in terms of activated monoamine neurotransmitters (Dishman et al., 1997), hippocampal parvalbumin expression (Arida et al., 2004), hippocampal BDNF and synapsin-1 expression (Ploughman et al., 2005), longevity and body composition (Narath et al., 2001), taste aversion learning (Masaki and Nakajima, 2006) and open-field behavior (Burghardt et al., 2004).

CONCLUDING REMARKS

The research reviewed here has demonstrated that voluntary physical exercise and vPL, two totally non invasive procedures, share the remarkable capability to potentiate plasticity in the adult visual cortex, favoring recovering of visual functions in adult amblyopic rodents.

These procedures have a great potential for application to human subjects, and indeed vPL has been first introduced in clinical research and then modeled in rodents. On the contrary, the impact of physical exercise on amblyopic adults remains to be elucidated, with preliminary results in our laboratory showing a strong enhancement of visual cortical plasticity in healthy subjects after a period of voluntary physical activity (Lunghi and Sale, in press).

In parallel with experiments aimed at directly testing the effects of the proposed behavioral interventions in human patients, a number of still open questions should be addressed in the animal model to strengthen the transferability of the achieved results:

- Is it possible to induce recovery of visual functional in animals trained with vPL without performing reverse suture, i.e., in adult amblyopic subjects with both eyes open?
- Which is the impact of physical exercise or vPL on stereopsis abilities in amblyopic animals?
- Which is the role of selected classes of inhibitory interneurons in the beneficial effects elicited by physical or visual training?
- Are the effects of visual recovery persistent?
- Which are the molecular mechanisms underlying plasticity in exercised animals?

Future research should focus on these open issues.

REFERENCES

Antonini, A., and Stryker, M. P. (1998). Effect of sensory disuse on geniculate afferents to cat visual cortex. *Vis. Neurosci.* 15, 401–409. doi: 10.1017/s0952523898153105

Arida, R. M., Scorza, C. A., da Silva, A. V., Scorza, F. A., and Cavalheiro, E. A. (2004). Differential effects of spontaneous versus forced exercise in rats on the staining of parvalbumin-positive neurons in the hippocampal formation. *Neurosci. Lett.* 364, 135–138. doi: 10.1016/j.neulet.2004.03.086

Astle, A. T., McGraw, P. V., and Webb, B. S. (2011). Can human amblyopia be treated in adulthood?. *Strabismus* 19, 99–109. doi: 10.3109/09273972.2011.600420

Ball, K., and Sekuler, R. (1982). A specific and enduring improvement in visual motion discrimination. *Science* 218, 697–698. doi: 10.1126/science.7134968

Ball, K., and Sekuler, R. (1987). Direction-specific improvement in motion discrimination. *Vision Res.* 27, 953–965. doi: 10.1016/0042-6989(87)90011-3

Bao, S., Chan, V. T., and Merzenich, M. M. (2001). Cortical remodelling induced by activity of ventral tegmental dopamine neurons. *Nature* 412, 79–83. doi: 10.1038/35083586

Baro, J. A., Lehmkuhle, S., and Kratz, K. E. (1990). Electroretinograms and visual evoked potentials in long-term monocularly deprived cats. *Invest. Ophthalmol. Vis. Sci.* 31, 1405–1409.

Baroncelli, L., Bonaccorsi, J., Milanese, M., Bonifacino, T., Giribaldi, F., Manno, I., et al. (2012). Enriched experience and recovery from amblyopia in adult rats: impact of motor, social and sensory components. *Neuropharmacology* 62, 2388–2397. doi: 10.1016/j.neuropharm.2012.02.010

Baroncelli, L., Braschi, C., and Maffei, L. (2013). Visual depth perception in normal and deprived rats: effects of environmental enrichment. *Neuroscience* 236, 313–319. doi: 10.1016/j.neuroscience.2013.01.036

Baroncelli, L., Maffei, L., and Sale, A. (2011). New perspectives in amblyopia therapy on adults: a critical role for the excitatory/inhibitory balance. *Front. Cell. Neurosci.* 5:25. doi: 10.3389/fncel.2011.00025

Baroncelli, L., Sale, A., Viegi, A., Maya Vetencourt, J. F., De Pasquale, R., Baldini, S., et al. (2010). Experience-dependent reactivation of ocular dominance plasticity in the adult visual cortex. *Exp. Neurol.* 226, 100–109. doi: 10.1016/j.expneurol.2010.08.009

Barrett, B. T., Bradley, A., and McGraw, P. V. (2004). Understanding the neural basis of amblyopia. *Neuroscientist* 10, 106–117. doi: 10.1177/1073858403262153

Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., and Hensch, T. K. (2010). Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J. Neurosci.* 30, 14964–14971. doi: 10.1523/JNEUROSCI.4812-10.2010

Bear, M. F., and Singer, W. (1986). Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 320, 172–176. doi: 10.1038/320172a0

Beurdeley, M., Spatazza, J., Lee, H. H., Sugiyama, S., Bernard, C., Di Nardo, A. A., et al. (2012). Otx2 binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. *J. Neurosci.* 32, 9429–9437. doi: 10.1523/JNEUROSCI.0394-12.2012

Blakemore, C., Vital-Durand, F., and Garey, L. J. (1981). Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proc. R. Soc. Lond. B Biol. Sci.* 213, 399–423. doi: 10.1098/rspb.1981.0072

Bonaccorsi, J., Berardi, N., and Sale, A. (2014). Treatment of amblyopia in the adult: insights from a new rodent model of visual perceptual learning. *Front. Neural Circuits* 8:82. doi: 10.3389/fncir.2014.00082

Burghardt, P. R., Fulk, L. J., Hand, G. A., and Wilson, M. A. (2004). The effects of chronic treadmill and wheel running on behavior in rats. *Brain Res.* 1019, 84–96. doi: 10.1016/j.brainres.2004.05.086

Buzsaki, G., Bickford, R. R., Ponomareff, G., Thal, L. L., Mandel, R., and Gage, F. F. (1988). Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *J. Neurosci.* 8, 4007–4026.

Chung, S. T., Li, R. W., and Levi, D. M. (2006). Identification of contrast-defined letters benefits from perceptual learning in adults with amblyopia. *Vision Res.* 46, 3853–3861. doi: 10.1016/j.visres.2006.06.014

Chung, S. T., Li, R. W., and Levi, D. M. (2008). Learning to identify near-threshold luminance-defined and contrast-defined letters in observers with amblyopia. *Vision Res.* 48, 2739–2750. doi: 10.1016/j.visres.2008.09.009

Dishman, R. K., Renner, K. J., Youngstedt, S. D., Reigle, T. G., Bunnell, B. N., Burke, K. A., et al. (1997). Activity wheel running reduces escape latency and alters brain monoamine levels after footshock. *Brain Res. Bull.* 42, 399–406. doi: 10.1016/s0361-9230(96)00329-2

Fiorentini, A., and Berardi, N. (1980). Perceptual learning specific for orientation and spatial frequency. *Nature* 287, 43–44. doi: 10.1038/287043a0

Fiorentini, A., and Berardi, N. (1981). Learning in grating waveform discrimination: specificity for orientation and spatial frequency. *Vision Res.* 21, 1149–1158. doi: 10.1016/0042-6989(81)90017-1

Foley-Nolan, A., McCann, A., and O'Keefe, M. (1997). Atropine penalisation versus occlusion as the primary treatment for amblyopia. *Br. J. Ophthalmol.* 81, 54–57. doi: 10.1136/bjo.81.1.54

Frenkel, M. Y., Sawtell, N. B., Diogo, A. C., Yoon, B., Neve, R. L., and Bear, M. F. (2006). Instructive effect of visual experience in mouse visual cortex. *Neuron* 51, 339–349. doi: 10.1016/j.neuron.2006.06.026

Fu, Y., Kaneko, M., Tang, Y., Alvarez-Buylla, A., and Stryker, M. M. (2015). A cortical disinhibitory circuit for enhancing adult plasticity. *Elife* 4:e05558. doi: 10.7554/elife.05558

Fu, Y., Tucciarone, J. J., Espinosa, J. J., Sheng, N., Darcy, D. D., Nicoll, R. R., et al. (2014). A cortical circuit for gain control by behavioral state. *Cell* 13, 1139–1152. doi: 10.1016/j.cell.2014.01.050

Gilbert, C. D., and Li, W. (2013). Top-down influences on visual processing. *Nat. Rev. Neurosci.* 14, 350–363. doi: 10.1038/nrn3476

Goard, M., and Dan, Y. (2009). Basal forebrain activation enhances cortical coding of natural scenes. *Nat. Neurosci.* 12, 1444–1449. doi: 10.1038/nn.2402

Green, C. C., and Bavelier, D. (2012). Learning, attentional control and action video games. *Curr. Biol.* 22, R197–R206. doi: 10.1016/j.cub.2012.02.012

Harauzov, A., Spolidoro, M., DiCristo, G., De Pasquale, R., Cancedda, L., Pizzorusso, T., et al. (2010). Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity. *J. Neurosci.* 30, 361–371. doi: 10.1523/JNEUROSCI.2233-09.2010

Hasselmo, M. M., and Giocomo, L. L. (2006). Cholinergic modulation of cortical function. *J. Mol. Neurosci.* 30, 133–135. doi: 10.1385/JMN:30:1:133

He, H. Y., Ray, B., Dennis, K., and Quinlan, E. M. (2007). Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nat. Neurosci.* 10, 1134–1136. doi: 10.1038/nn1965

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* 6, 877–888. doi: 10.1038/nrn1787

Hess, R. F. (2001). Amblyopia: site unseen. *Clin. Exp. Optom.* 84, 321–336. doi: 10.1111/j.1444-0938.2001.tb06604.x

Holmes, J. M., and Clarke, M. P. (2006). Amblyopia. *Lancet* 367, 1343–1351. doi: 10.1016/S0140-6736(06)68581-4

Huang, C. B., Zhou, Y., and Lu, Z. L. (2008). Broad bandwidth of perceptual learning in the visual system of adults with anisometropic amblyopia. *Proc. Natl. Acad. Sci. U S A* 105, 4068–4073. doi: 10.1073/pnas.0800824105

Hubel, D. H., and Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* 206, 419–436. doi: 10.1113/jphysiol.1970.sp009022

Kaneko, M., and Stryker, M. M. (2014). Sensory experience during locomotion promotes recovery of function in adult visual cortex. *Elife* 3:e02798. doi: 10.7554/elife.02798

Kasamatsu, T., and Pettigrew, J. D. (1976). Depletion of brain catecholamines: failure of ocular dominance shift after monocular occlusion in kittens. *Science* 194, 206–209. doi: 10.1126/science.959850

Kilgard, M. P., and Merzenich, M. M. (1998). Cortical map reorganization enabled by nucleus basalis activity. *Science* 279, 1714–1718. doi: 10.1126/science.279.5357.1714

Kratz, K. E., Mangel, S. C., Lehmkuhle, S., and Sherman, M. (1979). Retinal X- and Y-cells in monocularly lid-sutured cats: normality of spatial and temporal properties. *Brain Res.* 172, 545–551. doi: 10.1016/0006-8993(79)90586-9

Lee, A. A., Hoy, J. J., Bonci, A., Wilbrecht, L., Stryker, M. M., and Niell, C. C. (2014). Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. *Neuron* 83, 455–466. doi: 10.1016/j.neuron.2014.06.031

Levi, D. M. (2005). Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Dev. Psychobiol.* 46, 222–232. doi: 10.1002/dev.20050

Levi, D. D., and Li, R. W. (2009). Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res.* 49, 2535–2549. doi: 10.1016/j.visres.2009.02.010

Levi, D. M., and Polat, U. (1996). Neural plasticity in adults with amblyopia. *Proc. Natl. Acad. Sci. U S A* 93, 6830–6834. doi: 10.1073/pnas.93.13.6830

Levi, D. M., Polat, U., and Hu, Y. S. (1997). Improvement in Vernier acuity in adults with amblyopia. Practice makes better. *Invest. Ophthalmol. Vis. Sci.* 38, 1493–1510.

Lewis, T. L., and Maurer, D. (2009). Effects of early pattern deprivation on visual development. *Optom. Vis. Sci.* 86, 640–646. doi: 10.1097/opx.0b013e3181a7296b

Li, R. W., and Levi, D. M. (2004). Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *J. Vis.* 4, 476–487.

Li, R. R., Ngo, C., Nguyen, J., and Levi, D. D. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biol.* 9:e1001135. doi: 10.1371/journal.pbio.1001135

Li, R. R., Provost, A., and Levi, D. D. (2007). Extended perceptual learning results in substantial recovery of positional acuity and visual acuity in juvenile amblyopia. *Invest. Ophthalmol. Vis. Sci.* 48, 5046–5051. doi: 10.1167/iovs.07-0324

Li, R. R., Young, K. K., Hoenig, P., and Levi, D. D. (2005). Perceptual learning improves visual performance in juvenile amblyopia. *Invest. Ophthalmol. Vis. Sci.* 46, 3161–3168. doi: 10.1167/iovs.05-0286

Li, W., Piech, V., and Gilbert, C. C. (2008). Learning to link visual contours. *Neuron* 57, 442–451. doi: 10.1016/j.neuron.2007.12.011

Lunghi, C., and Sale, A. (in press). A cycling lane for brain rewiring. *Curr. Biol.*

Masaki, T., and Nakajima, S. (2006). Taste aversion in rats induced by forced swimming, voluntary running, forced running and lithium chloride injection treatments. *Physiol. Behav.* 88, 411–416. doi: 10.1016/j.physbeh.2006.04.013

Maya Vetencourt, J. F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O. F., et al. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* 320, 385–388. doi: 10.1126/science.1150516

McKee, S. P., and Westheimer, G. (1978). Improvement in vernier acuity with practice. *Percept. Psychophys.* 24, 258–262. doi: 10.3758/bf03206097

Metherate, R., Cox, C. C., and Ashe, J. J. (1992). Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. *J. Neurosci.* 12, 4701–4711.

Montey, K. K., and Quinlan, E. E. (2011). Recovery from chronic monocular deprivation following reactivation of thalamocortical plasticity by dark exposure. *Nat. Commun.* 2:317. doi: 10.1038/ncomms1312

Morishita, H., Miwa, J. M., Heintz, N., and Hensch, T. K. (2010). Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science* 330, 1238–1240. doi: 10.1126/science.1195320

Moruzzi, G., and Magoun, H. H. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.* 1, 455–473. doi: 10.1016/0013-4694(49)90219-9

Movshon, J. A., and Dürsteler, M. R. (1977). Effects of brief periods of unilateral eye closure on the kitten's visual system. *J. Neurophysiol.* 40, 1255–1265.

Narath, E., Skalicky, M., and Viidik, A. (2001). Voluntary and forced exercise influence the survival and body composition of ageing male rats differently. *Exp. Gerontol.* 36, 1699–1711. doi: 10.1016/s0531-5565(01)00145-0

Niell, C. C., and Stryker, M. M. (2010). Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65, 472–479. doi: 10.1016/j.neuron.2010.01.033

Olson, C. R., and Freeman, R. D. (1975). Progressive changes in kitten striate cortex during monocular vision. *J. Neurophysiol.* 38, 26–32.

Pediatric Eye Disease Investigator Group (2002). A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch. Ophthalmol.* 120, 268–278. doi: 10.1001/archopht.120.3.268

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J. J., and Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 298, 1248–1251. doi: 10.1126/science.1072699

Pizzorusso, T., Medini, P., Landi, S., Baldini, S., Berardi, N., and Maffei, L. (2006). Structural and functional recovery from early monocular deprivation in adult rats. *Proc. Natl. Acad. Sci. U S A* 103, 8517–8522. doi: 10.1073/pnas.0602657103

Ploughman, M., Granter-Button, S., Chernenko, G., Tucker, B. A., Mearow, K. M., and Corbett, D. (2005). Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin-like growth factor I after focal ischemia. *Neuroscience* 136, 991–1001. doi: 10.1016/j.neuroscience.2005.08.037

Polat, U., Ma-Naim, T., Belkin, M., and Sagi, D. (2004). Improving vision in adult amblyopia by perceptual learning. *Proc. Natl. Acad. Sci. U S A* 101, 6692–6697. doi: 10.1073/pnas.0401200101

Putignano, E., Lonetti, G., Cancedda, L., Ratto, G., Costa, M., Maffei, L., et al. (2007). Developmental downregulation of histone posttranslational modifications regulates visual cortical plasticity. *Neuron* 53, 747–759. doi: 10.1016/j.neuron.2007.02.007

Recanzone, G. H., Jenkins, W. M., Hradek, G. T., and Merzenich, M. M. (1992). Progressive improvement in discriminative abilities in adult owl monkeys performing a tactile frequency discrimination task. *J. Neurophysiol.* 67, 1015–1030.

Recanzone, G. H., Schreiner, C. E., and Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J. Neurosci.* 13, 87–103.

Rioult-Pedotti, M. S., Friedman, D., and Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science* 290, 533–536. doi: 10.1126/science.290.5491.533

Rioult-Pedotti, M. S., Friedman, D., Hess, G., and Donoghue, J. P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nat. Neurosci.* 1, 230–234. doi: 10.1038/678

Rodriguez, R., Kallenbach, U., Singer, W., and Munk, M. M. (2004). Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *J. Neurosci.* 24, 10369–10378. doi: 10.1523/jneurosci.1839-04.2004

Rogan, M. T., Staubli, U. V., and LeDoux, J. E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390, 604–607.

Sale, A., Berardi, N., and Maffei, L. (2014). Environment and brain plasticity: towards an endogenous pharmacotherapy. *Physiol. Rev.* 94, 189–234. doi: 10.1152/physrev.00036.2012

Sale, A., De Pasquale, R., Bonaccorsi, J., Pietra, G., Olivieri, D., Berardi, N., et al. (2011). Visual perceptual learning induces long-term potentiation in the visual cortex. *Neuroscience* 172, 219–225. doi: 10.1016/j.neuroscience.2010.10.078

Sale, A., Maya Vetencourt, J. F., Medini, P., Cenni, M. C., Baroncelli, L., De Pasquale, R., et al. (2007). Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat. Neurosci.* 10, 679–681. doi: 10.1038/nn1899

Sato, H., Hata, Y., Masui, H., and Tsumoto, T. (1987). A functional role of cholinergic innervation to neurons in the cat visual cortex. *J. Neurophysiol.* 58, 765–780.

Scali, M., Baroncelli, L., Cenni, M. M., Sale, A., and Maffei, L. (2012). A rich environmental experience reactivates visual cortex plasticity in aged rats. *Exp. Gerontol.* 47, 337–341. doi: 10.1016/j.exger.2012.01.007

Schummers, J., Sharma, J., and Sur, M. (2005). Bottom-up and top-down dynamics in visual cortex. *Prog. Brain Res.* 149, 65–81. doi: 10.1016/s0079-6123(05)49006-8

Sherman, S. M., and Stone, J. (1973). Physiological normality of the retinal in visually deprived cats. *Brain Res.* 60, 224–230. doi: 10.1016/0006-8993(73)90861-5

Silingardi, D., Scali, M., Belluomini, G., and Pizzorusso, T. (2010). Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long-term monocular deprivation. *Eur. J. Neurosci.* 31, 2185–2192. doi: 10.1111/j.1460-9568.2010.07261.x

Sillito, A. A., and Kemp, J. J. (1983). Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Res.* 289, 143–155. doi: 10.1016/0006-8993(83)90015-x

Simons, K., Stein, L., Sener, E. C., Vitale, S., and Guyton, D. L. (1997). Full-time atropine, intermittent atropine and optical penalization and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology* 104, 2143–2155. doi: 10.1016/s0161-6420(97)30048-7

Southwell, D. G., Froemke, R. C., Alvarez-Buylla, A., Stryker, M. P., and Gandhi, S. S. (2010). Cortical plasticity induced by inhibitory neuron transplantation. *Science* 327, 1145–1148. doi: 10.1126/science.1183962

Stepanyants, A., Martinez, L. M., Ferecskó, A. S., and Kisvárday, Z. F. (2009). The fractions of short- and long-range connections in the visual cortex. *Proc. Natl. Acad. Sci. U S A* 106, 3555–3560. doi: 10.1073/pnas.0810390106

Stettler, D. D., Das, A., Bennett, J., and Gilbert, C. D. (2002). Lateral connectivity and contextual interactions in macaque primary visual cortex. *Neuron* 36, 739–750. doi: 10.1016/s0896-6273(02)01029-2

Sugiyama, S., Di Nardo, A. A., Aizawa, S., Matsuo, I., Volovitch, M., Prochiantz, A., et al. (2008). Experience-dependent transfer of Otx2 homeoprotein into the visual cortex activates postnatal plasticity. *Cell* 134, 508–520. doi: 10.1016/j.cell.2008.05.054

van Praag, H., Kempermann, G., and Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 1, 191–198. doi: 10.1038/35042057

Weinberger, N. N. (2007). Associative representational plasticity in the auditory cortex: a synthesis of two disciplines. *Learn. Mem.* 14, 1–16. doi: 10.1101/lm.421807

Whitlock, J. R., Heynen, A. J., Shuler, M. G., and Bear, M. F. (2006). Learning induces long-term potentiation in the hippocampus. *Science* 313, 1093–1097. doi: 10.1126/science.1128134

Wiesel, T. N., and Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* 26, 1003–1017.

Wu, C., and Hunter, D. G. (2006). Amblyopia: diagnostic and therapeutic options. *Am. J. Ophthalmol.* 141, 175–184. doi: 10.1016/j.ajo.2005.07.060

Yotsumoto, Y., Watanabe, T., and Sasaki, Y. (2008). Different dynamics of performance and brain activation in the time course of perceptual learning. *Neuron* 57, 827–833. doi: 10.1016/j.neuron.2008.02.034

Zhang, T. Y., and Meaney, M. J. (2010). Epigenetics and the environmental regulation of the genome and its function. *Annu. Rev. Psychol.* 61, 439–466, C431–433. doi: 10.1146/annurev.psych.60.110707.163625

Zhou, Y., Huang, C., Xu, P., Tao, L., Qiu, Z., Li, X., et al. (2006). Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Res.* 46, 739–750. doi: 10.1016/j.visres.2005.07.031

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

REVIEW
published: 27 July 2015
doi: 10.3389/fnbeh.2015.00192

Visual rehabilitation: visual scanning, multisensory stimulation and vision restoration trainings

Neil M. Dundon[1,2], Caterina Bertini[1,2]*, Elisabetta Làdavas[1,2], Bernhard A. Sabel[3] and Carolin Gall[3]

[1] Department of Psychology, University of Bologna, Bologna, Italy, [2] Centre for Studies and Research in Cognitive Neuroscience, University of Bologna, Cesena, Italy, [3] Medical Faculty, Institute of Medical Psychology, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany

Neuropsychological training methods of visual rehabilitation for homonymous vision loss caused by postchiasmatic damage fall into two fundamental paradigms: "compensation" and "restoration". Existing methods can be classified into three groups: Visual Scanning Training (VST), Audio-Visual Scanning Training (AViST) and Vision Restoration Training (VRT). VST and AViST aim at compensating vision loss by training eye scanning movements, whereas VRT aims at improving lost vision by activating residual visual functions by training light detection and discrimination of visual stimuli. This review discusses the rationale underlying these paradigms and summarizes the available evidence with respect to treatment efficacy. The issues raised in our review should help guide clinical care and stimulate new ideas for future research uncovering the underlying neural correlates of the different treatment paradigms. We propose that both local "within-system" interactions (i.e., relying on plasticity within peri-lesional spared tissue) and changes in more global "between-system" networks (i.e., recruiting alternative visual pathways) contribute to both vision restoration and compensatory rehabilitation, which ultimately have implications for the rehabilitation of cognitive functions.

Keywords: hemianopia, vision restoration training, audio-visual training, visual scanning training, neural plasticity

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Mario Treviño Villegas, Universidad de Guadalajara, Mexico
Olivier A. Coubard, CNS-Fed, France

Correspondence:
Caterina Bertini, Department of Psychology, University of Bologna, Viale Berti Pichat 5, Bologna 40127, Italy
caterina.bertini@unibo.it

Received: *14 March 2015*
Accepted: *09 July 2015*
Published: *27 July 2015*

Citation:
Dundon NM, Bertini C, Làdavas E, Sabel BA and Gall C (2015) Visual rehabilitation: visual scanning, multisensory stimulation and vision restoration trainings. Front. Behav. Neurosci. 9:192. doi: 10.3389/fnbeh.2015.00192

Introduction

Homonymous visual field defects (HVFD) are among the most serious deficits after cerebral artery stroke and traumatic brain injury (TBI) in adults (Bouwmeester et al., 2007). HVFD result from damage to the visual pathway behind the chiasma, i.e., posterior brain regions including the optic tract, optic radiation and visual cortex, typically with either complete or partial loss of visual perception in one half of the visual field. HVFD affect both eyes in a homonymous manner, i.e., the loss of vision is on the same side of the visual field in both eyes. HVFD affect 20–30% of individuals who suffer cerebrovascular infarction (Rossi et al., 1990).

In approximately 70% of cases, patients with HVFD present with parafoveal visual field sparing of the central five degrees which enables them to fixate centrally (Kerkhoff, 2000). Nonetheless, HVFD patients suffer enduring difficulties in their everyday lives, such as impaired reading, navigation, visual exploration (Bouwmeester et al., 2007), visual cognition and motor-control (Kerkhoff, 2000). Vision loss is also a key issue in more general neuropsychological diagnosis and rehabilitation of cognitive functions; for example, both psychometric testing and computer-based training methods require sufficient vision to detect and identify stimuli (such as words or numbers, e.g., Tsai and Wang, 2015). HVFD can therefore compromise occupational rehabilitation, further disabling work or domestic life (Kerkhoff, 2000; Bouwmeester et al., 2007; Gall et al., 2009). In fact, vision loss may also lead to wrong diagnoses, such as neglect or agnosia (Serino et al., 2014).

In adult patients with HVFD, a certain amount of spontaneous recovery of the visual field may occur in the first 2–3 months post-lesion (Zhang et al., 2006). However, such spontaneous recovery is usually partial and only occurs in 20–30% of cases (Zihl and von Cramon, 1985). After this early recovery phase, further spontaneous improvements are rare (though exceptions have been reported, see Poggel et al., 2001). Spontaneous HVFD recovery tends to occur primarily in the visual periphery (Kerkhoff, 2000), which may be explained by either the cortical magnification factor (CMF; i.e., the peripheral visual field is processed by a lower number of neurons, but with larger receptive fields, compared to the foveal space; Çelebisoy et al., 2011; Harvey and Dumoulin, 2011; Wu et al., 2012) or by recruitment of the undamaged retino-collicular extra-striate pathway, which preferentially processes stimuli from the periphery of the visual field, in addition to processing the perception of movement (for review, see Sabel et al., 2011b).

In general, however, there is no additional spontaneous recovery beyond the first few months, and the HVFD is considered to be permanent. As a consequence, since the late 70–80 s the combined efforts of neuropsychological research and clinical practice have sought to achieve HVDF improvements in the post-acute stage of recovery through visual rehabilitation (for early rehabilitation studies, see Ben-Yishay and Diller, 1981, 1993; Ducarne and Barbeau, 1981; Ducarne et al., 1981; for a review, see Coubard et al., 2014). In this perspective, the term visual rehabilitation (Kerkhoff, 2000; Zihl, 2010) refers to all the rehabilitation strategies aiming to improve hemianopic patients' independent living and quality of life, promoting functional restitution of the impaired visual function (restoration approaches), the acquisition of compensatory strategies relying on the intact functions (compensatory approaches) or the adaptation of the environment to the patient's impairment, through artificial devices (substitution approaches).

The substitution approach does not rely on the plastic cortical reorganization properties of the lesioned brain, but aims at replacing the lost vision by artificial (usually optical) means. Among others, substitution methodologies include prosthesis (Hossain et al., 2005), optical prisms that project the unseen visual sector into parts of the intact visual field (Bowers et al., 2008, 2012; O'Neill et al., 2011), and reading aids connected to television or personal computers (Virgili et al., 2013).

On the other hand, compensation of the visual field loss might be accomplished by improving the gaze field by training patients to make saccadic eye movements toward the blind hemifield (Zihl, 1995, 1999; Nelles et al., 2001; Roth et al., 2009). Indeed, the fundamental goal of compensatory approaches is to enhance saccadic responses and other oculomotor parameters. In contrast, restoration methods aim at increasing the sensitivity of residual tissue and expanding the visual field itself, by activating residual structures of the damaged visual field to strengthen their neuronal activity and synaptic plasticity. The latter can be accomplished by vision training of areas of residual vision (ARV) or by applying non-invasive brain current stimulation (reviewed by Sabel et al., 2011b). Findings from these studies challenge the prevailing view that post-acute vision loss is both permanent and unchangeable.

Compensatory and restorative approaches have become popular in the last two decades thanks to the continued expansion of findings demonstrating experience-dependent plastic reorganization in the human visual system (Karmarkar and Dan, 2006; Martins Rosa et al., 2013). Since the pioneering studies in animal models (Wiesel and Hubel, 1965; Gilbert and Wiesel, 1992; Eysel et al., 1999), recent data on humans have revealed several forms of plasticity, such as perceptual learning (Gilbert et al., 2001; Fahle and Poggio, 2002) and long-term adaptation (Webster, 2011), providing evidence that plastic reorganization remains largely functional in the adult human visual system. Notably, early studies revealed that tactile image projections could effectively substitute vision for object recognition, demonstrating cortical plastic reorganization in the visual system of blind individuals, since early studies revealing that tactile image projections could effectively substitute vision for object recognition (Bach-y-Rita et al., 1969). Furthermore, a growing amount of evidence demonstrates improved visual performance and enhanced activation of visual areas using non-invasive human-machine interfaces (i.e., sensory substitution devices), which transform visual information into auditory or tactile representations (Abboud et al., 2014; for a review: Maidenbaum et al., 2014).

In the present paper, we discuss three main contemporary paradigms of vision rehabilitation: Visual Scanning Training (VST), Audio-Visual Scanning Training (AViST), and Vision Restoration Training (VRT). We will present the rationale which has shaped these paradigms and detail their respective methodologies. We will then report the outcomes of each treatment, drawing upon the body of available literature and criticisms offered by alternative viewpoints. Finally, we will discuss emergent neuroimaging and electroencephalographic data which are beginning to uncover the neural mechanisms underlying these treatment approaches.

How Compensation and Restoration Approaches Differ

The main difference between compensation and restoration is that the former primarily aims to recruit alternative unaffected brain regions that can play a compensatory role in the visual process, whereas the latter relies on the notion that stimulation of areas of partial injury (represented by partially functioning regions of the visual field) might induce synaptic plasticity and thus improvement to lost visual functions. Restoration techniques aim at modifying the visual system itself by lowering the threshold of perception. There has been a vigorous and controversial debate about whether vision restoration is possible at all (Sabel and Trauzettel-Klosinksi, 2005). On the one hand several authors have presented evidence that vision restoration is possible by behavioral training that activates areas with lowered perceptual thresholds or inconsistent light detection

(Kasten et al., 1998, 2006; Hyvärinen et al., 2002; Sabel et al., 2004; Sabel and Trauzettel-Klosinksi, 2005; Sahraie et al., 2006; Bouwmeester et al., 2007; Vanni et al., 2010). On the other hand, the fundamental concept of a functional restoration of vision has been vigorously opposed by different authors who argue that compensatory methods are the only way to help HVFD patients (Reinhard et al., 2005; Glisson, 2006; Pelak et al., 2007; Roth et al., 2009). In fact, also approaches such as flicker training (belonging to the field of vision restoration) were reported as ineffective, though the authors failed to apply the stimulation adequately since residual vision was not tested at those positions that were used for flicker training (Roth et al., 2009). During flicker training, stimuli are typically presented deep within the blind field. However, the experimenter failed to ensure the presence of residual vision within the blind field before defining the positions for flicker stimulation. In other studies, flicker training consistently results in increased detection sensitivity even deep within the blind field (Hyvärinen et al., 2002; Sahraie et al., 2006; Vanni et al., 2010). However, as our discussion below shows, compensation and restoration are not mutually exclusive concepts and both are worthy of further study.

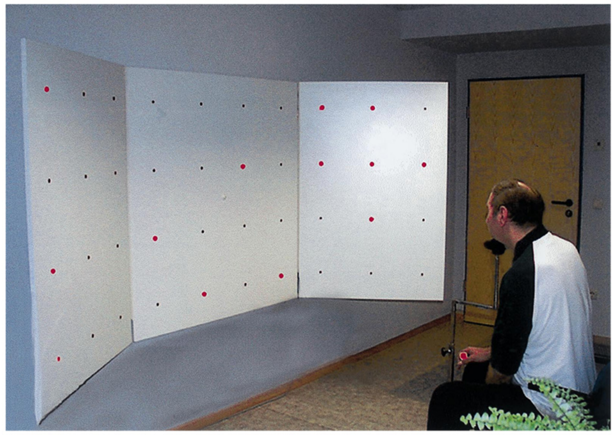


FIGURE 1 | Visual search task in Nelles et al. (2001). Patients were presented with simple red lights that were equally distributed across the board in four horizontal lines with ten lights in each line. The task was to identify a target stimulus (square of four lights) by exploratory eye movements with restricted head movements (with permission from Elsevier).

Compensation Training by VST

The term VST is used in this review to cover different types of unisensory (visual) eye movement training. The term "unisensory" refers to tasks which draw upon a single sensory modality, i.e., vision, in order to enhance visual functions; there is no ancillary recruitment of other senses (such as auditory or somatosensory cues as discussed below).

Compensatory approaches are oculomotor strategies which aim to train saccadic eye movements; thus, they do not specifically target the size of the scotoma but rather the field of view (i.e., the part of the visual scene that can be scanned by eye movements). Typically, this is accomplished by training patients to voluntarily (and consciously) explore arrays of visual stimuli—usually on computer screens (Zihl, 1995, 1999)—but stimuli may also be presented in far vision (Nelles et al., 2001; **Figure 1**). The rationale is to bias patients towards their blind hemifield in order to compensate for the restricted field of view resulting from the scotoma (Zihl, 1995). Indeed, HVFD patients do not spontaneously compensate for visual field loss, usually showing defective oculomotor behavior. Typically, patients perform more fixation and refixations compared to healthy controls and they show saccades with decreased amplitudes towards the hemianopic side, resulting in longer time of visual exploration (Meienberg et al., 1981; Pambakian et al., 2000). Therefore, by moving the eyes back and forth more often, the intact visual field sector then catches a greater area of the visual scene, increasing the so-called "field of view" (not to be confused with visual field enlargements achieved by vision restoration techniques). VST trains patients to make adaptive saccades into the affected blind field and systematically scan the visual scene in order to compensate for their loss by making better use of the intact visual field (Gassel and Williams, 1963; Ishiai et al., 1987). For example, if the vision loss is on the right, patients are taught to move their eyes more frequently to the right so that they may see objects more easily with their intact, left visual field sector.

Total training duration for VST is typically around 1 month, consisting of daily 1 h sessions. After about 5–6 weeks of VST, patients generally report improvements in scanning accuracy, exploration times and daily life activities (Kerkhoff et al., 1992, 1994; Zihl, 1995, 2000; Nelles et al., 2001; Pambakian et al., 2004; Verlohr and Dannheim, 2007; Mannan et al., 2010). However, notwithstanding these improvements, some concerns have been raised regarding the treatment's net-effects. When the size of the HVFD remains constant, which is the case in most VST studies, scanning more often towards the hemianopic side, e.g., to the right, results in a shift of the intact temporal visual field sector moving temporarily out of the field of view. In other words, developing a positive bias of moving the eyes more often towards the right means an automatic negative bias of not seeing objects on the left. Furthermore, increasing the volume of eye scanning also increases the integration load of the brain, as a larger amount of moving retinal images needs to be fused into a coherent object or motion; this increased load may be a problem for brains that suffer temporal processing and integration deficits (Schadow et al., 2009; Poggel et al., 2011).

Comparing the results of different VST studies is challenging, as different authors have experimented with different training protocols, varying either in the degree of cognitive demands or in the eccentricity of the field of view within which targets are presented. For example, Zihl (1995) introduced a simple visual detection task, requiring adult patients (mean age: 44 years) to shift their eyes towards the hemianopic field, after an acoustic signal, in order to find the visual target, i.e., a spot of light. Head movements were restricted as typical in these early VST studies (Zihl, 1995, 1999). Thus, early VST protocols only train oculomotor behavior for visual search in the range of near vision and the training area was reduced to a computer or television screen. A second phase of the training required patients to perform visual search tasks in a large stimulus array (52° × 45°). At the end of both phases of the training, visual search time markedly decreased and visual scanning behavior was better organized, showing a number of saccades and fixations similar to the one exhibited by healthy controls. In contrast, no change in the visual field size was observed. In a study by Nelles et al. (2001), VST was performed on a large display (3 m wide training board at a distance of 1.5 m) and adult patients (mean age: 59 years) were asked to systematically scan the board horizontally, to train saccades with restricted head movements. Performances after training revealed improved detection rate and reaction time to visual stimuli presented at the training board, when exploratory eye movements were allowed. In contrast, when exploratory eye movements were not allowed, no detection improvement was found. As in Zihl's (1995) study, VST resulted in a compensation of the HVFD without any measurable restoration of visual fields. It is worth noting that compensatory oculomotor strategies in HVFD patients also rely on working memory resources (Hardiess et al., 2010). Therefore, the training protocol recommended to patients should be chosen in accordance with the patient's performance level and availability of cognitive resources. The current trend is to develop visual tasks and training protocols with varying processing demands, presented on realistic, large field stimulus displays with unrestricted head movements, with simultaneous measurements of both head and eye movements. Papageorgiou et al. (2012) recently observed effective compensatory gaze patterns in patients with HVFD performing a more complex real life task (dynamic collision avoidance); these patterns include increased exploratory eye and head movements towards the blind side.

In summary, VST techniques offer a relatively short intervention with positive outcomes. Studies using similar VST paradigms to those described above (Zihl, 1995; Nelles et al., 2001) have found similar improvements in visual scanning behavior and visual detection with exploratory eye movements (Kerkhoff et al., 1994; Pambakian et al., 2004). More importantly, VST can also reduce the self-reported perceived disability of adult HVFD patients in daily activities, such as bumping into obstacles and crossing the street, thereby showing a transfer of training effects to ecological measures (Kerkhoff et al., 1994; Nelles et al., 2001). These effects can also promote successful return to work (Kerkhoff et al., 1994). Interestingly, age does not appear to be a critical factor in predicting the outcome of VST training: indeed, both older and younger adult patients achieve the same rehabilitation outcomes with the same amount of training (Schuett and Zihl, 2013). In addition, the beneficial results of VST remain stable as far as 8 months post treatment (Kerkhoff et al., 1994; Nelles et al., 2001).

AViST

AViST is the latest development in the field of compensatory interventions for visual field defects. In contrast to the classic compensatory interventions of VST which are unisensory, i.e., using only visual stimuli, AViST is multisensory. One advantage of AViST over VST, therefore, is the multisensory nature of the stimulation. Indeed, multisensory experience can adaptively maximize the sensory input options available to the organism when perceiving and localizing stimuli in the space.

Pioneering studies on animals (Stein and Meredith, 1993) have revealed the neurophysiological basis of multisensory integrative processes at the single neuron level, showing enhanced neural responses in the multisensory neurons of the superior colliculus (SC) when auditory and visual stimuli are in register, i.e., when presented in spatial and temporal coincidence (spatial and temporal principles of multisensory integration). Such enhanced neural responses are super-additive, i.e., the response to the combination of auditory and visual stimuli exceeds the sum of the responses to the single sensory stimulus (i.e., multisensory enhancement). Moreover, the effectiveness of the modality-specific signals is a major determinant of multisensory enhancement, with pairs of unisensory weakly effective stimuli resulting in more robust enhancement of the multisensory neuronal activity (i.e., the inverse efficacy principle; Stein and Stanford, 2008). A pivotal role in supporting the integrative processing in the SC has been demonstrated by heteromodal associative cortices in the cat (i.e., AES, rLS; Jiang et al., 2001; Jiang and Stein, 2003). In line with this finding, the inferior parietal (Dong et al., 1994) and intraparietal cortices (Colby et al., 1993; Duhamel et al., 1998; Schlack et al., 2002) have been suggested as sites of convergence of sensory information from many different modalities in primates. Additionally, imaging studies in humans have confirmed the involvement of the SC and posterior cortical areas, including the temporo-parietal and posterior parietal cortices, in mediating audio-visual multisensory integration (for a review: Calvert, 2001; Stein and Stanford, 2008).

Crucially, converging evidence also suggests the presence of multisensory benefits at the behavioral level, both in animals' orienting responses (Gingras et al., 2009) and in a wide range of perceptual tasks in humans (for review see: Alais et al., 2010). In particular, behavioral studies on healthy participants have shown that multisensory integrative mechanisms can improve both detection (Frassinetti et al., 2002; Bolognini et al., 2005a; Bertini et al., 2008; Leo et al., 2008a; Maravita et al., 2008) and localization (Hairston et al., 2003; Lovelace et al., 2003; Alais and Burr, 2004; Bolognini et al., 2007; Leo et al., 2008b; Bertini et al., 2010) of audio-visual pairs consisting of degraded unisensory stimuli. Interestingly, repeated exposure to coincident audio-visual pairs of stimuli effectively facilitates visual learning (Kim et al., 2008) and enhances activation in extrastriate cortical areas (Shams and Kim, 2012). More importantly, audio-visual integration can increase perceptual performances in patients with unisensory defects, such as HVFD or neglect (Frassinetti et al., 2005), low vision (Targher et al., 2012) or auditory localization deficits (Bolognini et al., 2007). In particular, visual detection of stimuli presented in the blind field of patients with HVFD was significantly improved by the presentation of spatio-temporal aligned audio-visual stimuli, while no improvement was found when stimuli were presented in spatial disparity or temporal asynchrony (Frassinetti et al., 2005).

As a consequence, the AViST model posits that audio-visual multisensory integration can be a useful resource for rehabilitation of unisensory visual defects, and that the recruitment of the retino-colliculo-extrastriate pathway, which is usually spared after post-chiasmatic lesions causing HVFD, can compensate for the loss of visual perception. In line with the inverse effectiveness principle, impaired unisensory processing in HVFD might be improved by multisensory stimulation. Indeed, multisensory neural circuits, retaining their responsiveness to cross-modal stimuli, might constitute the neural basis for the compensation of impaired sensory modalities (Làdavas, 2008).

Based on these multisensory principles, Bolognini et al. (2005b) developed a training protocol to determine whether systematic stimulation of the visual field over the course of a period of training with combined audio-visual stimuli would lead to long lasting amelioration of unisensory visual orientation and detection deficits in patients with chronic post-chiasmatic lesions. Training was administered by seating patients centrally at the concave face of an ellipse shaped apparatus in a horizontal arc in a dimly lit and sound-proof room (**Figure 2**). Eight piezoelectric loudspeakers were positioned along the eye-line at 8, 24, 40 and 56° of eccentricity towards the right and left side to present auditory stimuli (bursts of 100 ms of white noise). In addition, eight red LED lights were placed on the exact same position of the loudspeakers to present visual stimuli for 100 ms. During training, patients first fixated upon the central point of the arc (± 30° of vertical eccentricity respectively for inferior and superior quadrantopia), then explored the visual field by moving their eyes, not their heads. In each block, the patients were instructed to search for visual stimuli being presented alone (unisensory condition) or coupled with an auditory stimulus (multisensory condition). Lone auditory stimuli constituted a catch trial condition. Participants were encouraged to move their eyes left or right along the median line, exploring the visual field. Afterwards they were instructed that the sound might sometimes (but not always) be predictive of the location of the light. To boost oculomotor exploration of the hemianopic visual field, a greater proportion of stimuli was presented in the blind visual field—so that the patients learned to respond more easily to that side over time. Patients responded with button press after detection of a visual stimulus. Training duration was approximately 2 weeks at a rate of 4 h/working day. Patients completed training by achieving a hit-rate of >50%, i.e., consistently above chance level, in the unisensory visual condition in the blind field for one entire training session.

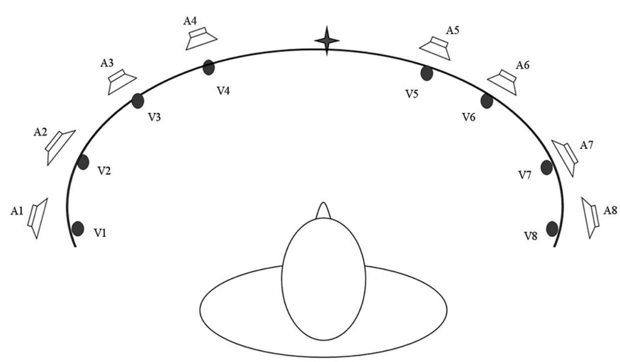


FIGURE 2 | A schematic bird's eye view of the apparatus used for the Audio-Visual Scanning Training (AViST), depicting the location of visual (V1–V8) and auditory (A1–A8) stimuli. Stimuli are positioned at 8, 24, 40 and 56 visual degrees into both the left and right visual field in an ellipse shaped apparatus (200 cm wide, 30 cm height).

After the treatment, HVFD patients (average lesion age: 12 months; mean age: 57 years) showed an increase of visual detections (without fixation requirement), improvements of visual search and reading abilities and a reduction in self-perceived disability in daily activities (such as bumping into obstacles, crossing the street, finding objects in an ecological environment). The improvements were stable at a 1 month follow-up (Bolognini et al., 2005b). In addition, Passamonti et al. (2009) revealed that the same treatment was also effective in a different sample of patients (average lesion age: 58.16 months; mean age: 43 years) in improving oculomotor parameters during visual search and reading tasks. In particular, all patients reported an improvement in oculomotor exploration after treatment, which was characterized by fewer fixations and refixations, faster and larger saccades, and a reduced scanpath length, leading to a shorter exploration time, compared to pre-treatment performances. Similarly, training significantly affected oculomotor reading parameters, reducing both progressive and regressive saccades. Further, the treatment drove improvements with respect to the specific reading impairments observed in both left and right hemisphere—damaged patients (Leff et al., 2000); saccadic amplitude increased for right hemianopic patients and the number of saccades during the return sweep reduced in left hemianopic patients (Passamonti et al., 2009). Notably, as in the Bolognini et al. (2005b) study, the training promoted a reduction in self-perceived disability in daily life activities, confirming a transfer of the effects of the training to ecological environments. In this study, improvements were stable at follow-up assessment, 1 year after training.

However, it is worth noting that the improvements were only seen in tasks where patients were able to use eye movements to compensate for the loss of their vision. Indeed, no amelioration was found in the visual detection task where patients fixated the central fixation cross. The discrepancy between the results of the tasks where exploratory eye movements were allowed and where they were not allowed (when central fixation was required) suggests that the improvement in visual perception induced by the training is not due to an enlargement of the visual field, but rather to an activation of the visual responsiveness of the oculomotor system, reinforcing orientation towards the blind hemifield.

Crucially, the amelioration cannot be attributed to a mere habituation effect whereby the training simply encourages saccades towards the hemianopic field; indeed, a similar training protocol, using unisensory visual stimuli instead of multisensory audio-visual stimuli, yielded no improvements in a control patient group (Passamonti et al., 2009). This finding suggests the multisensory nature of the stimulation is the critical factor inducing amelioration. It could also be argued that having two stimuli rather than one increases the overall attentional salience, i.e., the magnitude of training stimuli reaching the senses, in the hemianopic field and thus pulls the attention spotlight in this direction. In other words, the important component of the training is not its multisensory nature, but rather it simply works by having an increased magnitude of stimulation in the hemianopic field via two stimuli rather than only one. Though this cannot yet be ruled out conclusively, the observation that perception does not improve unless stimuli are spatially and temporally aligned as described above, i.e., conforming to multisensory principles, suggests that aggregation of attentional salience may not be a sufficient explanation of treatment effects. Interestingly, significant visual exploration and improvements in oculomotor parameters also occur in patients with recently acquired occipital lesions, after a similar compensatory audio-visual training in the acute post-stroke phase within 24 weeks after brain injury (Keller and Lefin-Rank, 2010). In line with previous evidence (Passamonti et al., 2009), patients showed greater oculomotor (i.e., an increased number and amplitude of saccades towards the hemianopic field) and compensatory visual scanning improvements after audio-visual stimulation, compared to unisensory visual stimulation, providing further evidence of the clinical advantages of a multisensory exploration training.

We propose that the training was effective at integrating sensory inputs from different sensory modalities related to the same external event, consequently enhancing the efficiency of eye saccades to the presentation of the visual stimulus. More specifically, it appears that repetitive audio-visual stimulation of the hemianopic field mediates an exogenous shift of multisensory attention in this direction, which strengthens oculomotor mechanisms to scan the hemianopic field more efficiently. Since patients with visual defects tend to direct the focus of their attention to the intact hemifield (Sabel et al., 2011b), the auditory cue interacting with visual input reverses this tendency by inducing an exogenous shift of multisensory spatial attention towards the blind hemifield.

We further propose that recruitment of the spared retino-colliculo-extrastriate pathway might drive this effect. Converging evidence reveals the pivotal role of the SC in integrating audio-visual spatio-temporal coincident stimuli in humans (Calvert et al., 2001; Bertini et al., 2008; Leo et al., 2008a; Maravita et al., 2008), and the relevance of temporo-parietal and posterior parietal cortices in mediating covert and overt orienting behavior towards audio-visual stimuli (Meienbrock et al., 2007; Bertini et al., 2010; Nardo et al., 2014). In addition, recent findings have provided evidence that after disruption of the primary visual cortex, the retino-colliculo-extrastriate pathway is functionally and anatomically spared and could foster orienting responses toward visual stimuli presented in the blind field (Tamietto et al., 2012). Intensive multisensory stimulation during training could have enhanced the activity of this network and allowed the implementation of more efficient oculomotor patterns due to stronger links between SC and other higher order cognitive areas, such as the frontal eye fields, which contribute to oculomotor planning (Arikuni et al., 1980; Barbas and Mesulam, 1985). In line, connections between the SC and the frontal eye fields are thought to join a neural circuit mediating spatial attention shifts (for a review: Krauzlis et al., 2013).

In summary, initial evidence suggests that combining different sensory modalities represents an effective training for visual field defects. However, further studies are needed to explore the neural underpinnings of the compensation of visual field defects after AViST.

Vision Restoration by VRT

According to the residual vision activation theory (Sabel et al., 2011b), cerebral visual injury is usually not complete, and some structures are typically spared in or near the area of damage. Such areas of spared neurons lie in different places in the brain: (i) in penumbral areas of partial damage at the border of the lesion; (ii) in islands of surviving tissue dispersed within the lesion; (iii) extrastriate pathways unaffected by the damage; and (iv) down-stream, higher-level neuronal networks. The functional status of these structures is likely to be compromised because the damaged visual system suffers an enduring tripartite handicap: (i) partially damaged areas have fewer neurons; (ii) they lack sufficient attentional resources; and (iii) neurons in areas of partial damage have poor firing synchrony. Residual structures therefore no longer contribute (or contribute rather little) to every-day vision and their silencing through non-use further impairs their synaptic strength.

The VRT approach posits that such partially spared regions of cortex are functionally represented by ARV. More specifically, visual field deficits do not produce an absolute, binary split between areas of total blindness and areas of intact vision (the black-and-white view of vision loss), separated by a sharp and clearly definable visual field border. Rather, visual field defects actually comprise: (i) areas of total blindness; (ii) areas of consistent (normal) visual detection; and (iii) areas where visual detection performance is present but inconsistent.

Typically, visual field charts are based on applying standard static near-threshold perimetry using a low resolution stimulus presentation, presented in a monocular fashion. However, due to the rather low resolution, these perimetric tasks are not sensitive enough to decipher smaller regions of inconsistent (partial) visual detection. Standard near-threshold testing methods predominantly delineate areas of vision loss vs. intact vision while the topography of the ARV which is typically located at the border zone along the defect remains unclear. By increasing the number of test positions it is theoretically possible to gain the missing information by means of near-threshold perimetry. However, this procedure is not used in clinical settings since it results in a tremendous increase in test duration. Supra-threshold high resolution perimetry (HRP) has therefore been used to test detection of light stimuli binocularly within a dense grid of stimulus presentations. This greater sensitivity has assisted with both the characterization of distinct regions of ARV, and the evaluation of treatment effects (Kasten et al., 1998).

The presence of ARV and VRT effects have been considered to be artifacts of inaccurate diagnostic measurements resulting from poor fixation because of excessive eye movements (Reinhard et al., 2005; Glisson, 2006). However, good fixation abilities are a prerequisite for VRT. Furthermore, ARVs can be very well replicated across repeated measurements and eye tracker recordings show that the standard deviation of the mean fixation point in patients with homonymous hemianopia is about 0.82° horizontally and 1.16° before VRT (Kasten et al., 2006).

Increasing evidence gathered with HRP suggests that patients with cerebral visual injuries have ARV of varying sizes, typically at the transition between areas of total blindness and areas of normal visual detection, i.e., at the visual field border, or in islands of residual vision within the areas of total blindness. To plan VRT sessions, these ARV regions are first identified so that they can then be activated to enhance the function of underlying partially spared neuronal tissue. It is hypothesized that VRT re-engages these residual structures by repetitive stimulation and activation of ARV. The residual vision activation theory posits that when a certain minimum number of neurons remains connected to their target structure, they can lay the foundation for neuroplastic reorganization via synaptic plasticity and subsequent functional improvement following VRT in HVFD patients with chronic lesions (Sabel et al., 2011b) just as in normal perceptual learning (Li et al., 2004; Fahle, 2005). Animal studies are compatible with this hypothesis; a relatively small number of intact cells (10–20%) can support spontaneous recovery up to 70–80% normal performance in simple visual detection in rats within 2–3 weeks post-lesion (Sautter and Sabel, 1993).

VRT can induce visual perception improvement at any time after the lesion, at all ages and in all types of visual field impairments after retinal or brain damage (such as stroke, brain trauma etc.). Concerning the influence of age on VRT outcomes, Kasten et al. (2000) could not reproduce earlier results from a VRT pilot study pointing to an effect of age on visual field enlargement (Kasten and Sabel, 1995). In fact, in a large clinical observational study with a sample size of more than 300 subjects, patients aged 65 years and older benefited more from VRT than younger patients (Mueller et al., 2007).

If and to what extent vision restoration can be achieved is a function of the amount of residual tissue and its activation state, and of the status of global neuronal networks (Sabel et al., 2011b). Sustained improvements require repetitive stimulation which, depending on the method, may take days (non-invasive brain stimulation; Fedorov et al., 2011; Sabel et al., 2011a; Gall et al., 2013; Schmidt et al., 2013) or months (behavioral training with VRT; Kasten et al., 1998; Poggel et al., 2004; Sabel et al., 2004). By becoming re-engaged in every day vision, (re)activation of ARV by VRT outlasts the training period, thus contributing to lasting vision restoration and improvements in quality of life (Gall et al., 2008).

Drawing on this new understanding, methodologies were developed to accurately identify ARV, and train these areas according to individualized protocols of VRT. Kasten et al. (1997) described a collection of computer programs utilized in VRT. Participants' visual field defects are first evaluated using HRP performed on a computer screen in a dimly lit room. During HRP, small light spots appear with luminance well above physiological thresholds in random order in a dense grid of 25 × 19 stimulus positions surrounding a central fixation point. Subjects respond to any perception of these light spots. Fixation is ascertained by the accurate response to an isoluminant change in color of the fixation point. The tested visual field covers up to 20 visual degrees both vertically and horizontally. **Figure 3** shows a HRP visual field chart in which white squares graphically illustrate normal visual detection performance. In contrast, black squares reflect areas of zero detection and gray areas indicate ARV where responses were present, but inconsistent (**Figure 3**).

After delineating residual function (i.e., identifying the ARV), the training procedure is individually adapted to the patient's specific deficit pattern. VRT is developed to specifically target ARV with the goal of strengthening these structures by repetitive activation. This is achieved by presentation of localized "static" stimuli along the visual field border or "dynamic" stimuli which appear first in either the blind or intact field and move to the nearest point in the ARV (Kasten et al., 1997). Patients respond to each perceived stimulus via button press. The training protocol is adaptive—when the detection performance exceeds a pre-determined point, typically, greater than 90% correct responses, the computer programme advances to the next level by presenting stimuli deeper within the blind field. Training usually takes place in the participant's home for 30–60 min per day, for a period of at least 6 months. The central outcome measure after VRT is light detection accuracy change as observed in HRP (**Figure 3**) or standard-automated perimetry procedures. In sum, the treatment is effective at driving improvements with the majority of patients, by an average visual field border shift of 5° of visual angle (Kasten et al., 1998). Improvements have also been reported to generalize to some extent to visual exploration tasks (Kasten et al., 1998; Reinhard et al., 2005). Notably, patients also report subjective improvements in ecological environments (Kasten et al., 1998; Julkunen et al., 2003; Reinhard et al., 2005). The positive outcomes of VRT appear stable up to 23 months after the training (Kasten et al., 2001; Julkunen et al., 2003; Marshall et al., 2008; Poggel et al., 2010). According to different reviews (Bouwmeester et al., 2007; Sabel et al., 2011b), some patients do not benefit from VRT (33%), moderate improvements are seen in about 33% and large field expansions in another 33% percent of the patients. Of a total number of 37 publications, all but three confirmed the efficacy of the VRT paradigm (Sabel et al., 2011b). The non-confirmatory studies, however, suffered from methodological limitations; one limitation is that the training duration was too short and the training stimuli too small to achieve clinically relevant effects (Balliet et al., 1985). In another case, insensitive methods of measuring visual detections were employed (Sabel et al., 2004; Reinhard et al., 2005). The third study failed to focus the therapy on ARV but rather used a simple flickering stimulus which was presented deep in the blind field where no residual structures were present (Roth et al., 2009). Thus, the latter study actually did not use the typical VRT-treatment protocol as other studies did.

As mentioned above, some authors have raised doubts about the validity of VRT (e.g., Reinhard et al., 2005; Glisson, 2006; Bouwmeester et al., 2007; Pelak et al., 2007). The argument

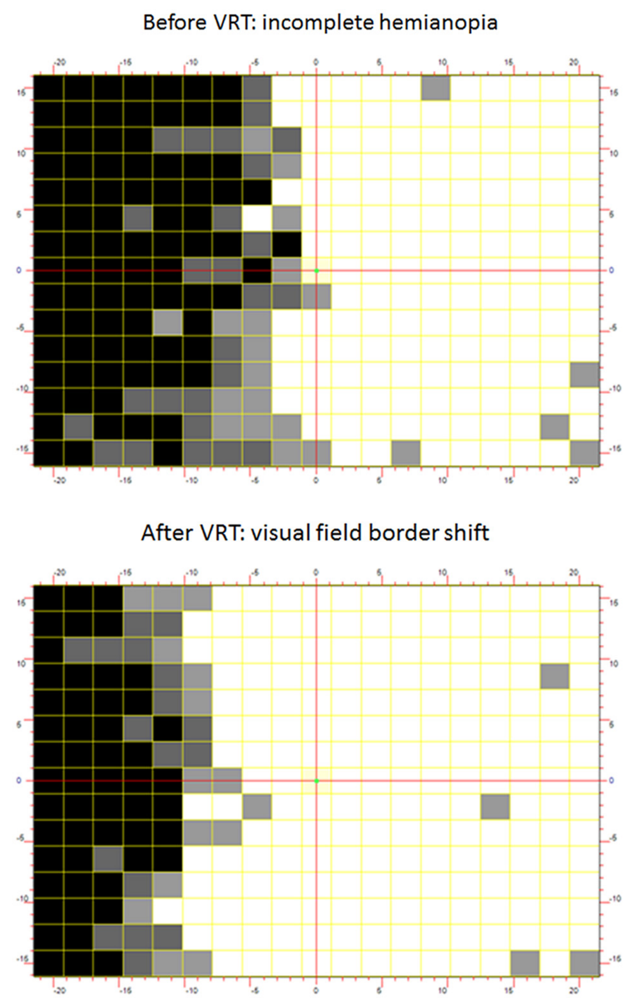


FIGURE 3 | (Upper panel) Baseline-Vision Restoration Training (VRT) visual field chart. To assess the visual fields with high-resolution computer-based perimetry, suprathreshold stimuli are presented at random from which simple detection charts can be created. By superimposing results of repeated tests, intact visual field sectors are shown in white and black represents regions of absolute blindness where no stimulus detections occurred. Gray areas reveal areas of residual vision (ARV) where response accuracy is inconsistent. Area of residual vision correspond to relative defects in standard-automated perimetry and may be interpreted as representing partial damage where only some cells remain connected with their target structure. Thus, partial structure leads to partial function. **(Lower panel)** The chart depicts the Post-VRT result in the same subject. The visual field defect has resolved mainly within the area of residual vision at baseline.

is that plasticity is not possible in the visual system and that visual field improvement after VRT is merely a compensation artifact in disguise, i.e., that increased eye movements explain the visual field improvement. However, this compensation artifact claim can be rejected for several reasons (Kasten et al., 2006; Sabel et al., 2011b). Firstly, it stands to reason that if training improvement was merely a function of random lateral fluctuating saccades, there could not be a systematic shift of the border in one direction, as consistently documented. On this point, some authors have suggested that the treatment effect is systematically biased by the lateral saccades, i.e., preferential scanning towards the hemianopic side in evaluation tests. However, this response bias would require patients to be able to predict the (randomly chosen) position of the transient evaluation stimuli during post-treatment testing which is logically and practically impossible. In addition, good fixation ability is a prerequisite for training, which dismisses propositions that results are confounded by eccentric fixation. Further, treatment does not appear to change the position of the blind-spot (for more detail, see Sabel et al., 2011b).

Recent evidence also adds to these logical arguments. For example, training does not always cause a shift of the entire visual field border. Quite often shifts only occur in one sector of the border (for example in the upper visual field). Further, post-training visual field border shifts for patients with concentric visual field loss, as in glaucoma, typically move in a ring-like fashion in all directions towards the periphery (Gudlin et al., 2008; Sabel and Gudlin, 2014). Additionally, eye movements are not directionally specific (before or after treatment), blind spot positions do not appear to shift, and eye movement amplitudes after VRT actually decrease, suggesting a post-training improvement in fixation quality (Kasten et al., 2006). More recent studies have also availed of eye-movement adjusted retinal charts observing new stimulus detections after VRT in previously blind areas of the visual field (Sabel et al., 2011b). Thus, while the eye is not expected to be exactly at fixation at all times—since microsaccades are a normal repertoire of visual perception (Ahissar and Arieli, 2012)—both experimental evidence and logical reasoning rules out eye movements as explaining improvements following vision restoration, though they are always a possible source of variability and, respectively, error, in visual field testing. In summary, many independent studies show the efficacy of VRT in achieving visual field improvements (Kasten et al., 1998; Sabel et al., 2004; Poggel et al., 2006; Henriksson et al., 2007; Gudlin et al., 2008; Marshall et al., 2008; Romano et al., 2008; Ho et al., 2009; Halko et al., 2011; Plow et al., 2012).

VRT does not appear to drive change solely in the visual cortex. Ho et al. (2009) used retinotopic mapping when analysing residual function after VRT and observed responses in extrastriate areas above the calcarine sulcus. Functional Magnectic Resonance Imaging (fMRI) studies of the Blood Oxygen Level Dependent (BOLD) change following VRT have also observed increased post-training activations in anterior cingulate and dorsolateral frontal cortex, in addition to the recruitment of higher order visual areas in the occipitotemporal and middle temporal regions (Marshall et al., 2008). Henriksson et al. (2007) further observed ipsilateral representation of the trained visual hemifield in different cortical areas, including the primary visual cortex. Thus, the emerging evidence suggests that VRT drives plastic cortical reorganization both at the within-systems and the network level, i.e., training drives activation increases not only in occipital regions but also in wider distributed attention networks. In fact, this concept of global network change has most recently been demonstrated by electroencephalography (EEG) network analyses in optic nerve patients treated with non-invasive brain current stimulation which also improved patients' visual fields (Bola et al., 2014).

Discussion

The evidence presented in this review supports the idea that visual rehabilitation, defined as the promotion of improvements in independent living and quality of life, can be achieved with adult HVFD patients using either VST, AViST or VRT (Kerkhoff, 2000; Pambakian et al., 2005; Schofield and Leff, 2009; Zihl, 2010; Trauzettel-Klosinski, 2011; de Haan et al., 2014; Goodwin, 2014). The reviewed studies suggest that VST and AViST induce long term improvements in patients' visual exploration abilities, promoting a more organized pattern of fixations and refixations and increasing the amplitude of the saccades (Zihl, 1995; Nelles et al., 2001; Bolognini et al., 2005b; Passamonti et al., 2009). In contrast, VRT reportedly induces an average visual field border shift of 5 degrees of visual angle (Kasten et al., 1998). Although VST, AViST and VRT promote different visual functions, all three approaches have been demonstrated to generalize the positive outcomes observed with clinical measurements also to daily life activities (Kerkhoff et al., 1994; Kasten et al., 1998; Nelles et al., 2001; Julkunen et al., 2003; Bolognini et al., 2005b; Reinhard et al., 2005; Passamonti et al., 2009; Dundon et al., in press).

Since on first appraisal VST, AViST and VRT appear to seek different outcomes, they seem to fall under separate and specific rehabilitation models—restoration (VRT) vs. compensation (VST), or a compensation/restoration hybrid (AViST).

In general terms, restorative therapies aim at improving the magnitude of visual function, while VST and AViST compensate for the visual field loss. However, in terms of the neural mechanisms underlying the two approaches, each of these two ostensibly disparate treatment methodologies may well draw on both, local and distal, cortical reorganization mechanisms. This suggests that in case of visual rehabilitation, concepts of restoration and compensation can be both fluid and reciprocal. Broadly speaking, neuroplastic changes can be indexed into two categories, delineated by the associated lesion proximity and overall diffusivity of cortical reorganization. The first model, within systems plasticity, targets reconnection of damaged neural circuits proximal to, or within islands of spared tissue surrounded by the lesion (Robertson and Murre, 1999; Sabel et al., 2011b). The second model, network level plasticity, refers to recruitment of more widespread processes of cortical reorganization, such as homologous areas in the intact hemisphere or alternative spared pathways subserving the visual function (Sabel et al., 2011b), in order to compensate for loss of specific neuronal function (Bola et al., 2014).

Within the context of visual rehabilitation following brain injury, within-systems plasticity would target functional restoration of partially spared cortex within or near the striate or extra-striate lesion, i.e., repairing neurons to re-engage them in their previous function; this model would appear to best describe the plastic reorganization driven by VRT. Conversely, network level plasticity recruits alternative networks to compensate for the lost function within a different specific area, i.e., the visual cortex; this model would appear to best describe the change elicited by VST and AViST. Apparently, the above axis appears to neatly compartmentalize the three treatments presented in this paper. However, the emerging findings from studies attempting to document the underlying substrate change driven by these therapies seem to contradict such a simple binary hypothesis.

Concerning VRT, fMRI studies have revealed effects within wider distributed networks, i.e., BOLD changes occur not only in the visual cortex, but also in extrastriate areas (Henriksson et al., 2007; Marshall et al., 2008; Ho et al., 2009). In a similar vein, the notion that treatment improvements driven by VST are exclusively driven by compensatory eye movements has been challenged by some recent experimental findings. For example, eye-movement training not only induces plasticity within oculomotor brain areas but it also alters brain activation in the striate and extrastriate cortex (Nelles et al., 2007, 2009, 2010), i.e., in areas where VRT was also observed to induce activation changes (Marshall et al., 2008). In line, Kerkhoff et al. (1992) observed a visual field border shift following a period of VST, raising the question of to what extent the functional improvements in compensatory training may, in fact, be at least in part the consequence of vision restoration. As far as AViST is concerned, the retino-colliculo-extrastriate pathway is a possible neural substrate mediating its visual exploration and oculomotor improvements. Indeed, the colliculo-extrastriate pathway is crucial in integrating audio-visual information in humans (for a review: Stein and Stanford, 2008) and is known to be functionally spared in patients with Primary Visual Cortex (V1) lesions (Tamietto et al., 2012). In line, recent evidence in animals suggests that a systematic audio-visual training can reinstate visual behavior in hemianopic cats, after a lesion to the striate cortex (Jiang et al., 2015). Crucially, such recovery co-occurs with the reinstatement of visual responsiveness in deep layer neurons of the ipsilesional SC. Therefore, audio-visual stimulation may enhance activity within this spared network, and recruit additional cortical areas responsible for oculomotor planning, such as the frontal eye fields, which are known to be strongly connected to the SC and to be involved in spatial orienting behaviors (for a review: Krauzlis et al., 2013). However, similar to VST, and in addition to network-level plasticity, AViST might also elicit neural restoration in the occipital cortex, since eye movements are known to lower the perceptual threshold. Indeed, both in primates and humans, the visual system uses saccades as a preferred sampling strategy (Martinez-Conde et al., 2004, 2009; Otero-Millan et al., 2008; Troncoso et al., 2008; Rolfs, 2009), which allows more efficient sampling of fine spatial detail (Donner and Hemilä, 2007) and elicits stronger responses in V1 neurons (Martinez-Conde et al., 2000, 2002; Herrington et al., 2009). In fact, this point can also be made with regard to VST.

In any event, the neural correlates underlying improvements after each form of treatment need further investigation, which would be relevant both from a theoretical and clinical point of view. Theoretically, the investigation of the neural bases of visual field recovery might provide more useful information about neural plasticity mechanisms after lesions. From a within-systems plasticity perspective, given the diversity observed in patients with brain lesions, it is important to know the location and magnitude of intact neuronal tissue required for different treatment modalities to have a positive effect. Similarly, at a network plasticity level, it is imperative to understand what functional network level circuitry is necessary to assist with training effects or other stimulation approaches such as those using alternating currents (Bola et al., 2014). At the clinical level, this knowledge will be useful to predict the outcome of each type of treatment. Based on this understanding one could choose the most effective treatment procedure for individual patients, possibly incorporating a combination of treatments, with the aim of optimizing improvements in visual rehabilitation.

In addition, attentional processes and the mechanisms regulating training improvements in VST, AViST and VRT deserve special interest, as they appear to serve as a key area of theoretical overlap between the treatment approaches. Presumably, HVFD patients typically direct their focus of attention to the intact field, reinforcing an attention pattern that favors the intact field section and ignores ARV. Shifting attention towards the intact field might, on the one hand, reduce neural activation in partially defective regions of the visual cortex, i.e., ARV, while, on the other hand, oculomotor exploration of the blind field may diminish. Indeed, attentional cues presented in the blind field boost the effects of VRT (Poggel et al., 2004), suggesting that attention potentiates visual rehabilitation. In this study, a special cueing procedure was administered during VRT to help patients shift their focus of attention towards a certain area located at the visual field border and deeper in the blind field. Visual detection improved especially in those parts of the visual field where the cue was presented (Poggel et al., 2004).

Similarly, recent EEG evidence (Dundon et al., in press), collected before and after AViST, suggests that an attention shift occurs during the training. In addition to improvements on the previously listed behavioral measures, AViST also drove a reduction in P300 components in response to stimuli presented in the healthy field during a simple visual detection task. This neurophysiological effect likely reflects a reduced allocation of attention towards the intact visual field after training. Interestingly, Marshall et al. (2008) who studied BOLD change following VRT, noticed activation reductions in the right inferior and middle temporal, medial frontal, and bilateral basal ganglia, when a group of right-hemianopic (i.e., intact right hemisphere) participants responded to stimuli in their healthy visual field. No reductions occurred in the left hemisphere, suggesting that activation reductions appeared to be restricted to the healthy hemisphere. Promising early signs of network-level neuroplastic overlap between VRT and AViST are therefore emerging, specifically within the domain of attentional rebalancing.

Another area of interest for future research is the application of non-invasive brain stimulation to boost the efficacy of the rehabilitative techniques. Emerging evidence supports the efficacy of using non-invasive brain current stimulation in the treatment of visual impairments after optic nerve lesions and HVFD (Halko et al., 2011; Sabel et al., 2011a; Plow et al., 2012; Gall et al., 2013; Schmidt et al., 2013). Recent studies have demonstrated that combining VRT with transcranial direct current stimulation (tDCS) applied to posterior occipital regions may enhance the effect of VRT without tDCS (Plow et al., 2012). In the case of tDCS, stimulation appears to give impetus to excitability changes in visual cortex and other brain structures (Antal et al., 2006). Studies using EEG power-spectra analysis have described significant increases in alpha-activity, localized to occipital sites, following repetitive, transorbital alternating current stimulation (rtACS; Schmidt et al., 2013). Non-invasive stimulation, therefore, seems to elicit increased neuronal network synchronization which is substantiated by lasting bilateral synchronous waves in alpha and theta ranges in central and occipital brain areas (Sabel et al., 2011a) and restore lost functional connectivity networks in the brain (Bola et al., 2014). Concerning VRT as an independent method, it still needs to be shown whether neuronal network synchronization, i.e., increases of spectral coherence in the visual cortex but also in wider distributed networks, serves as a mechanism of action.

In summary, the field of visual rehabilitation is at a promising junction. Both compensatory and restorative technologies have become available for the treatment of HVFD and possibly other types of visual field defects. It will be important to further delineate what the common elements between the approaches are, and what makes each one unique. Furthermore, the techniques should be standardized to compare results between laboratories and results should be made available to the medical community to ascertain best practice clinical care.

Importantly, the three reviewed approaches differ in terms of time on task (intensity) and duration. Indeed, VST training procedures usually last 5–6 weeks with daily 1 h sessions, the AViST training has a duration of 2 weeks with daily 4 h sessions, while the VRT approach consists of a 3–6 months training with daily 30 min sessions. Despite these duration differences, they each operate within an adaptive framework. Recent evidence supports adaptive treatments in order to ensure that patients are consistently challenged without being overly frustrated or fatigued by task demands, which is optimal for both maximising clinical outcome and avoiding patient drop outs (Klingberg, 2010). Indeed, the reported drop-out rates of these approaches seem to be negligible: Pambakian et al. (2004) reported a drop-out of two out of 29 patients during a VST training, due to aggravated clinical and social conditions, while the other studies do not mention any case of drop-outs.

Broadly speaking, visual rehabilitation targeting restoration of a portion of the visual field, seems to represent an optimal approach to address visual field function and size. However, VRT consists of a long-lasting training protocol, which may not suit the life circumstances of all patients. Although there were no reports of drop outs or an extremely low rate in those VRT studies that were conducted in a laboratory setting (e.g., Kasten et al., 1998; Mueller et al., 2007; Gudlin et al., 2008), clinical experience dictates that time-consuming training protocols may constitute a reason for dropping out in some patients. Here, faster methods of non-invasive brain stimulation may offer a complementary or alternative solution. In addition, from an ecological perspective, improvements at the visual field border may not be sufficient to completely recover impairments in daily life activities. For those still suffering everyday life impariments despite having been treated with restoration techniques, compensatory approaches, such as VST or AViST, might help overcome these limitations.

Only by considering evidence from all fields of study, and employing an open, critical debate, can we make the fastest possible progress to help patients with partial blindness. Further, we should not simply consider local events at the lesion site or immediately around it, but also study the visual system in a holistic manner, including global brain network function, saccade-induced facilitations, cross- and/or multimodal influences and attentional mechanisms. Thus, by considering the topic in a holistic way we can serve both research needs and clinical necessities in a manner that is not microscopic but macro-scopic with the ultimate goal to optimize clinical care in vision rehabilitation.

Acknowledgments

This research was supported by grants from the Ministero Istruzione Università e Ricerca (PRIN) to EL and from the Federal German Education and Research Ministry grant "Restoration of Vision after Stroke (REVIS)" (ERA-net Neuron, BMBF 01EW1210) to BAS and CG.

References

Abboud, S., Hanassy, S., Levy-Tzedek, S., Maidenbaum, S., and Amedi, A. (2014). EyeMusic: introducing a "visual" colorful experience for the blind using auditory sensory substitution. *Restor. Neurol. Neurosci.* 32, 247–257. doi: 10.3233/RNN-130338

Ahissar, E., and Arieli, A. (2012). Seeing via miniature eye movements: a dynamic hypothesis for vision. *Front. Comput. Neurosci.* 6:89. doi: 10.3389/fncom.2012.00089

Alais, D., and Burr, D. (2004). The ventriloquist effect results from near-optimal bimodal integration. *Curr. Biol.* 14, 257–262. doi: 10.1016/s0960-9822(04)00043-0

Alais, D., Newell, F. N., and Mamassian, P. (2010). Multisensory processing in review: from physiology to behaviour. *Seeing Perceiving* 23, 3–38. doi: 10.1163/187847510x488603

Antal, A., Nitsche, M. A., and Paulus, W. (2006). Transcranial direct current stimulation and the visual cortex. *Brain Res. Bull.* 68, 459–463. doi: 10.1016/j.brainresbull.2005.10.006

Arikuni, T., Sakai, M., Hamada, I., and Kubota, K. (1980). Topographical projections from the prefrontal cortex to the post-arcuate area in the rhesus monkey, studied by retrograde axonal transport of horseradish peroxidase. *Neurosci. Lett.* 19, 155–160. doi: 10.1016/0304-3940(80)90187-1

Bach-y-Rita, P., Collins, C. C., Saunders, F. A., White, B., and Scadden, L. (1969). Vision substitution by tactile image projection. *Nature* 221, 963–964. doi: 10.1038/221963a0

Balliet, R., Blood, K. M., and Bach-y-Rita, P. (1985). Visual field rehabilitation in the cortically blind? *J. Neurol. Neurosurg. Psychiatry* 48, 1113–1124. doi: 10.1136/jnnp.48.11.1113

Barbas, H., and Mesulam, M. M. (1985). Cortical afferent input to the principalis region of the rhesus monkey. *Neuroscience* 15, 619–637. doi: 10.1016/0306-4522(85)90064-8

Ben-Yishay, Y., and Diller, L. (1981). Rehabilitation of cognitive and perceptual defects in people with traumatic brain damage. *Int. J. Rehabil. Res.* 4, 208–210. doi: 10.1097/00004356-198106000-00012

Ben-Yishay, Y., and Diller, L. (1993). Cognitive remediation in traumatic brain injury: update and issues. *Arch. Phys. Med. Rehabil.* 74, 204–213.

Bertini, C., Leo, F., Avenanti, A., and Làdavas, E. (2010). Independent mechanisms for ventriloquism and multisensory integration as revealed by theta-burst stimulation. *Eur. J. Neurosci.* 31, 1791–1799. doi: 10.1111/j.1460-9568.2010.07200.x

Bertini, C., Leo, F., and Làdavas, E. (2008). Temporo-nasal asymmetry in multisensory integration mediated by the Superior Colliculus. *Brain Res.* 1242, 37–44. doi: 10.1016/j.brainres.2008.03.087

Bola, M., Gall, C., Moewes, C., Fedorov, A., Hinrichs, H., and Sabel, B. A. (2014). Brain functional connectivity network breakdown and restoration in blindness. *Neurology* 83, 542–551. doi: 10.1212/wnl.0000000000000672

Bolognini, N., Frassinetti, F., Serino, A., and Làdavas, E. (2005a). "Acoustical vision" of below threshold stimuli: interaction among spatially converging audiovisual inputs. *Exp. Brain Res.* 160, 273–282. doi: 10.1007/s00221-004-2005-z

Bolognini, N., Leo, F., Passamonti, C., Stein, B. E., and Làdavas, E. (2007). Multisensory-mediated auditory localization. *Perception* 36, 1477–1485. doi: 10.1068/p5846

Bolognini, N., Rasi, F., Coccia, M., and Làdavas, E. (2005b). Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain.* 128, 2830–2842. doi: 10.1093/brain/awh656

Bouwmeester, L., Heutink, J., and Lucas, C. (2007). The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 78, 555–564. doi: 10.1136/jnnp.2006.103853

Bowers, A. R., Keeney, K., and Peli, E. (2008). Community-based trial of a peripheral prism visual field expansion device for hemianopia. *Arch. Ophthalmol.* 126, 657–664. doi: 10.1001/archopht.126.5.657

Bowers, A. R., Tant, M., and Peli, E. (2012). A pilot evaluation of on-road detection performance by drivers with hemianopia using oblique peripheral prisms. *Stroke Res. Treat.* 2012:176806. doi: 10.1155/2012/176806

Calvert, G. A. (2001). Crossmodal processing in the human brain: insights from functional neuroimaging studies. *Cereb. Cortex* 11, 1110–1123. doi: 10.1093/cercor/11.12.1110

Calvert, G. A., Hansen, P. C., Iversen, S. D., Brammer, M. J. (2001). Detection of audio-visual integration sites in humans by application of electrophysiological criteria to the BOLD effect. *Neuroimage* 14, 427–438. doi: 10.1006/nimg.2001.0812

Çelebisoy, M., Çelebisoy, N., Bayam, E., and Köse, T. (2011). Recovery of visual-field defects after occipital lobe infarction: a perimetric study. *J. Neurol. Neurosurg. Psychiatry* 82, 695–702. doi: 10.1136/jnnp.2010.214387

Colby, C. L., Duhamel, J. R., and Goldberg, M. E. (1993). Ventral intraparietal area of the macaque: anatomic location and visual response properties. *J. Neurophysiol.* 69, 902–914.

Coubard, O. A., Urbanski, M., Bourlon, C., and Gaumet, M. (2014). Educating the blind brain: a panorama of neural bases of vision and of training programs in organic neurovisual deficits. *Front. Integr. Neurosci.* 8:89. doi: 10.3389/fnint.2014.00089

de Haan, G. A., Heutink, J., Melis-Dankers, B. J., Tucha, O., and Brouwer, W. H. (2014). Spontaneous recovery and treatment effects in patients with homonymous visual field defects: a meta-analysis of existing literature in terms of the ICF framework. *Surv. Ophthalmol.* 59, 77–96. doi: 10.1016/j.survophthal.2013.02.006

Dong, W. K., Chudler, E. H., Sugiyama, K., Roberts, V. J., and Hayashi, T. (1994). Somatosensory, multisensory and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J. Neurophysiol.* 72, 542–564.

Donner, K. O., and Hemilä, S. O. (2007). Modelling the effect of microsaccades on retinal responses to stationary contrast patterns. *Vision Res.* 47, 1166–1177. doi: 10.1016/j.visres.2006.11.024

Ducarne, B., and Barbeau, M. (1981). [Techniques for examination and rehabilitation of patients with visual disturbances of cerebral origin (author's transl)]. *Rev. Neurol. (Paris)* 137, 693–707.

Ducarne, B., Bergego, C., and Barbeau, M. (1981). [Restitution of visual function in two cases of post-anoxic occipital blindness: a long term clinical study (author's transl)]. *Rev. Neurol. (Paris)* 137, 741–784.

Duhamel, J. R., Colby, C. L., and Goldberg, M. E. (1998). Ventral intraparietal area of the macaque: congruent visual and somatic response properties. *J. Neurophysiol.* 79, 126–136.

Dundon, N., Làdavas, E., Maier, M. E., and Bertini, C. (in press). Multisensory stimulation in hemianopic patients boosts orienting responses to the hemianopic field and reduces attentional resources to the intact field. *Restor. Neurol. Neurosci.* in press. doi: 103233/RNN-140457

Eysel, U. T., Schweigart, G., Mittmann, T., Eyding, D., Qu, Y., Vandesande, F., et al. (1999). Reorganization in the visual cortex after retinal and cortical damage. *Restor. Neurol. Neurosci.* 15, 153–164.

Fahle, M. (2005). Perceptual learning: specificity versus generalization. *Curr. Opin. Neurobiol.* 15, 154–160. doi: 10.1016/j.conb.2005.03.010

Fahle, M., and Poggio, T. (2002). *Perceptual Learning.* Cambridge: Bradford books.

Fedorov, A., Jobke, S., Bersnev, V., Chibisova, A., Chibisova, Y., Gall, C., et al. (2011). Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. *Brain Stimul.* 4, 189–201. doi: 10.1016/j.brs.2011.07.007

Frassinetti, F., Bolognini, N., Bottari, D., Bonora, A., and Làdavas, E. (2005). Audiovisual integration in patients with visual deficit. *J. Cog. Neurosci.* 17, 1442–1452. doi: 10.1162/0898929054985446

Frassinetti, F., Bolognini, N., and Làdavas, E. (2002). Enhancement of visual perception by crossmodal visuo-auditory interaction. *Exp. Brain Res.* 147, 332–343. doi: 10.1007/s00221-002-1262-y

Gall, C., Antal, A., and Sabel, B. A. (2013). Non-invasive electrical brain stimulation induces vision restoration in patients with visual pathway damage. *Graefes Arch. Clin. Exp. Ophthalmol.* 251, 1041–1043. doi: 10.1007/s00417-012-2084-7

Gall, C., Lucklum, J., Sabel, B. A., and Franke, G. H. (2009). Vision and health-related quality of life in patients with visual field loss after postchiasmatic lesions. *Invest. Ophthalmol. Vis. Sci.* 50, 2765–2776. doi: 10.1167/iovs.08-2519

Gall, C., Mueller, I., Gudlin, J., Lindig, A., Schlueter, D., Jobke, S., et al. (2008). Vision and health-related quality of life before and after vision restoration training in cerebrally damaged patients. *Restor. Neurol. Neurosci.* 26, 341–353.

Gassel, M. M., and Williams, D. (1963). Visual function in patients with homonymous hemianopia II. Oculo-motor mechanisms. *Brain* 86, 1–36. doi: 10.1093/brain/86.1.1

Gilbert, C. D., Sigman, M., and Crist, R. E. (2001). The neural basis of perceptual learning. *Neuron* 31, 681–697. doi: 10.1016/s0896-6273(01)00424-x

Gilbert, C. D., and Wiesel, T. N. (1992). Receptive field dynamics in adult primary visual cortex. *Nature* 356, 150–152. doi: 10.1038/356150a0

Gingras, G., Rowland, B. A., and Stein, B. E. (2009). The differing impact of multisensory and unisensory integration on behavior. *J. Neurosci.* 29, 4897–4902. doi: 10.1523/jneurosci.4120-08.2009

Glisson, C. C. (2006). Capturing the benefit of vision restoration therapy. *Curr. Opin. Ophthalmol.* 17, 504–508. doi: 10.1097/icu.0b013e328010852e

Goodwin, D. (2014). Homonymous hemianopia: challenges and solutions. *Clin. Ophthalmol.* 8, 1919–1927. doi: 10.2147/opth.s59452

Gudlin, J., Mueller, I., Thanos, S., and Sabel, B. A. (2008). Computer based vision restoration therapy in glaucoma patients: a small open pilot study. *Restor. Neurol. Neurosci.* 26, 403–412.

Hairston, W. D., Laurienti, P. J., Mishra, G., Burdette, J. H., and Wallace, M. T. (2003). Multisensory enhancement of localization under conditions of induced myopia. *Exp. Brain Res.* 152, 404–408. doi: 10.1007/s00221-003-1646-7

Halko, M. A., Datta, A., Plow, E. B., Scaturro, J., Bikson, M., and Merabet, L. B. (2011). Neuroplastic changes following rehabilitative training correlate with regional electrical field induced with tDCS. *Neuroimage* 57, 885–891. doi: 10.1016/j.neuroimage.2011.05.026

Hardiess, G., Papageorgiou, E., Schiefer, U., and Mallot, H. A. (2010). Functional compensation of visual field deficits in hemianopic patients under the influence of different task demands. *Vision Res.* 50, 1158–1172. doi: 10.1016/j.visres.2010.04.004

Harvey, B. M., and Dumoulin, S. O. (2011). The relationship between cortical magnification factor and population receptive field size in human visual cortex: constancies in cortical architecture. *J. Neurosci.* 31, 13604–13612. doi: 10.1523/jneurosci.2572-11.2011

Henriksson, L., Raninen, A., Näsänen, R., Hyvärinen, L., and Vanni, S. (2007). Training induced cortical representation of a hemianopic field. *J. Neurol. Neurosurg. Psychiatry* 78, 74–81. doi: 10.1136/jnnp.2006.099374

Herrington, T. M., Masse, N. Y., Hachmeh, K. J., Smith, J. E. T., Assad, J. A., and Cook, E. P. (2009). The effect of microsaccades on the correlation between neural activity and behavior in middle temporal, ventral intraparietal and lateral intraparietal areas. *J. Neurosci.* 29, 5793–5805. doi: 10.1523/jneurosci.4412-08.2009

Ho, Y. C., Cheze, A., Sitoh, Y. Y., Petersen, E. T., Goh, K. Y., Gjedde, A., et al. (2009). Residual neurovascular function and retinotopy in a case of hemianopia. *Ann. Acad. Med. Singapore* 38, 827–831.

Hossain, P., Seetho, I. W., Browning, A. C., and Amoaku, W. M. (2005). Artificial means for restoring vision. *BMJ* 330, 30–33. doi: 10.1136/bmj.330.7481.30

Hyvärinen, L., Raninen, A. N., and Näsänen, R. E. (2002). Vision rehabilitation in homonymous hemianopia. *Neuroophthalmology* 27, 97–102. doi: 10.1076/noph.27.1.97.14292

Ishiai, S., Furukawa, T., and Tsukagoshi, H. (1987). Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect. *Neuropsychologia* 25, 675–679. doi: 10.1016/0028-3932(87)90058-3

Jiang, W., and Stein, B. E. (2003). Cortex controls multisensory depression in superior colliculus. *J. Neurophysiol.* 90, 2123–2135. doi: 10.1152/jn.00369.2003

Jiang, H., Stein, B. E., and McHaffie, J. G. (2015). Multisensory training reverses midbrain lesion-induced changes and ameliorates haemianopia. *Nat. Commun.* 6:7263. doi: 10.1038/ncomms8263

Jiang, W., Wallace, M. T., Jiang, H., Vaughan, J. W., and Stein, B. E. (2001). Two cortical areas mediate multisensory integration in superior colliculus neurons. *J. Neurophysiol.* 85, 506–522.

Julkunen, L., Tenovuo, O., Jääskeläinen, S. K., and Hämäläinen, H. (2003). Rehabilitation of chronic post-stroke visual field defect with computer-assisted training: a clinical and neurophysiological study. *Restor. Neurol. Neurosci.* 21, 19–28.

Karmarkar, U. R., and Dan, Y. (2006). Experience-dependent plasticity in adult visual cortex. *Neuron* 52, 577–585. doi: 10.1016/j.neuron.2006.11.001

Kasten, E., Bunzenthal, U., and Sabel, B. A. (2006). Visual field recovery after vision restoration therapy (VRT) is independent of eye movements: an eye tracker study. *Behav. Brain Res.* 175, 18–26. doi: 10.1016/j.bbr.2006.07.024

Kasten, E., Müller-Oehring, E., and Sabel, B. A. (2001). Stability of visual field enlargements following computer-based restitution training—Results of a follow-up. *J. Clin. Exp. Neuropsychol.* 23, 297–305. doi: 10.1076/jcen.23.3.297.1180

Kasten, E., Poggel, D. A., and Sabel, B. A. (2000). Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. *J. Cogn. Neurosci.* 12, 1001–1012. doi: 10.1162/08989290051137530

Kasten, E., and Sabel, B. A. (1995). Visual field enlargement after computer training in brain-damaged patients with homonymous deficits: an open pilot trial. *Restor. Neurol. Neurosci.* 8, 113–127. doi: 10.3233/RNN-1995-8302

Kasten, E., Strasburger, H., and Sabel, B. A. (1997). Programs for diagnosis and therapy of visual field deficits in vision rehabilitation. *Spat. Vis.* 10, 499–503. doi: 10.1163/156856897x00456

Kasten, E., Wüst, S., Behrens-Baumann, W., and Sabel, B. A. (1998). Computer-based training for the treatment of partial blindness. *Nat. Med.* 4, 1083–1087. doi: 10.1038/2079

Keller, I., and Lefin-Rank, G. (2010). Improvement of visual search after audiovisual exploration training in hemianopic patients. *Neurorehabil. Neural Repair* 24, 666–673. doi: 10.1177/1545968310372774

Kerkhoff, G. (2000). Neurovisual rehabilitation: recent developments and future directions. *J. Neurol. Neurosurg. Psychiatry* 68, 691–706. doi: 10.1136/jnnp.68.6.691

Kerkhoff, G., Münßinger, U., Haaf, E., Eberle-Strauss, G., and Stögerer, E. (1992). Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. *Restor. Neurol. Neurosci.* 4, 245–254. doi: 10.3233/RNN-1992-4402

Kerkhoff, G., Münssinger, U., and Meier, E. K. (1994). Neurovisual rehabilitation in cerebral blindness. *Arch. Neurol.* 51, 474–481. doi: 10.1001/archneur.1994.00540170050016

Kim, R. S., Seitz, A. R., and Shams, L. (2008). Benefits of stimulus congruency for multisensory facilitation of visual learning. *PLoS One* 3:e1532. doi: 10.1371/journal.pone.0001532

Klingberg, T. (2010). Training and plasticity of working memory. *Trends Cogn. Sci.* 14, 317–324. doi: 10.1016/j.tics.2010.05.002

Krauzlis, R. J., Lovejoy, L. P., and Zénon, A. (2013). Superior colliculus and visual spatial attention. *Annu. Rev. Neurosci.* 36, 165–182. doi: 10.1146/annurev-neuro-062012-170249

Làdavas, E. (2008). Multisensory-based approach to the recovery of unisensory deficit. *Ann. N Y Acad. Sci.* 1124, 98–110. doi: 10.1196/annals.1440.008

Leff, A. P., Scott, S. K., Crewes, H., Hodgson, T. L., Cowey, A., Howard, D., et al. (2000). Impaired reading in patients with right hemianopia. *Ann. Neurol.* 47, 171–178. doi: 10.1002/1531-8249(200002)47:2<171::aid-ana6>3.3.co;2-g

Leo, F., Bertini, B., di Pellegrino, G., and Làdavas, E. (2008a). Multisensory integration for orienting responses in humans requires the activation of the superior colliculus. *Exp. Brain Res.* 186, 67–77. doi: 10.1007/s00221-007-1204-9

Leo, F., Bolognini, N., Passamonti, C., Stein, B. E., and Làdavas, E. (2008b). Cross-modal localization in hemianopia: new insights on multisensory integration. *Brain* 131, 855–865. doi: 10.1093/brain/awn003

Li, W., Piëch, V., and Gilbert, C. D. (2004). Perceptual learning and top-down influences in primary visual cortex. *Nat. Neurosci.* 7, 651–657. doi: 10.1038/nn1255

Lovelace, C. T., Stein, B. E., and Wallace, M. T. (2003). An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Brain Res. Cogn. Brain Res.* 17, 447–453. doi: 10.1016/s0926-6410(03)00160-5

Maidenbaum, S., Abboud, S., and Amedi, A. (2014). Sensory substitution: closing the gap between basic research and widespread practical visual rehabilitation. *Neurosci. Biobehav. Rev.* 41, 3–15. doi: 10.1016/j.neubiorev.2013.11.007

Mannan, S. K., Pambakian, A. L., and Kennard, C. (2010). Compensatory strategies following visual search training in patients with homonymous hemianopia: an eye movement study. *J. Neurol.* 257, 1812–1821. doi: 10.1007/s00415-010-5615-3

Maravita, A., Bolognini, N., Bricolo, E., Marzi, C. A., and Savazzi, S. (2008). Is audiovisual integration subserved by the superior colliculus in humans? *Neuroreport* 19, 271–275. doi: 10.1097/wnr.0b013e3282f4f04e

Marshall, R. S., Ferrera, J. J., Barnes, A., Zhang, X., O'Brien, K. A., Chmayssani, M., et al. (2008). Brain activity associated with stimulation therapy of the visual borderzone in hemianopic stroke patients. *Neurorehabil. Neural Repair* 22, 136–144. doi: 10.1177/1545968307305522

Martinez-Conde, S., Macknik, S. L., and Hubel, D. H. (2000). Microsaccadic eye movements and firing of single cells in the striate cortex of macaque monkeys. *Nat. Neurosci.* 3, 251–258. doi: 10.1038/72961

Martinez-Conde, S., Macknik, S. L., and Hubel, D. H. (2002). The function of bursts of spikes during visual fixation in the awake primate lateral geniculate nucleus and primary visual cortex. *Proc. Natl. Acad. Sci. U S A* 99, 13920–13925. doi: 10.1073/pnas.212500599

Martinez-Conde, S., Macknik, S. L., and Hubel, D. H. (2004). The role of fixational eye movements in visual perception. *Nat. Rev. Neurosci.* 5, 229–240. doi: 10.1038/nrn1348

Martinez-Conde, S., Macknik, S. L., Troncosco, X. G., and Hubel, D. H. (2009). Microsaccades: a neurophysiological analysis. *Trends Neurosci.* 32, 463–475. doi: 10.1016/j.tins.2009.05.006

Martins Rosa, A., Silva, M. F., Ferreira, S., Murta, J., and Castelo-Branco, M. (2013). Plasticity in the human visual cortex: an ophthalmology-based perspective. *Biomed. Res. Int.* 2013:568354. doi: 10.1155/2013/568354

Meienberg, O., Zangemeister, W. I. I., Rosenberg, M., Hoyt, W. F., and Stark, L. (1981). Saccadic eye movement strategies in patients with homonymous hemianopia. *Ann. Neurol.* 9, 537–544. doi: 10.1002/ana.410090605

Meienbrock, A., Naumer, M. J., Doehrmann, O., Singer, W., and Muckli, L. (2007). Retinotopic effects during spatial audio-visual integration. *Neuropsychologia* 45, 531–539. doi: 10.1016/j.neuropsychologia.2006.05.018

Mueller, I., Mast, H., and Sabel, B. A. (2007). Recovery of visual field defects: a large clinical observational study using vision restoration therapy. *Restor. Neurol. Neurosci.* 25, 563–572.

Nardo, D., Santangelo, V., and Macaluso, E. (2014). Spatial orienting in complex audiovisual environments. *Hum. Brain Mapp.* 35, 1597–1614. doi: 10.1002/hbm.22276

Nelles, G., de Greiff, A., Pscherer, A., Stude, P., Forsting, M., Hufnagel, A., et al. (2007). Saccade induced cortical activation in patients with post-stroke visual field defects. *J. Neurol.* 254, 1244–1252. doi: 10.1007/s00415-007-0511-1

Nelles, G., Esser, J., Eckstein, A., Tiede, A., Gerhard, H., and Diener, H. C. (2001). Compensatory visual field training for patients with hemianopia after stroke. *Neurosci. Lett.* 306, 189–192. doi: 10.1016/s0304-3940(01)01907-3

Nelles, G., Pscherer, A., de Greiff, A., Forsting, M., Gerhard, H., Esser, J., et al. (2009). Eye-movement training-induced plasticity in patients with post-stroke hemianopia. *J. Neurol.* 256, 726–733. doi: 10.1007/s00415-009-5005-x

Nelles, G., Pscherer, A., de Greiff, A., Gerhard, H., Forsting, M., Esser, J., et al. (2010). Eye-movement training-induced changes of visual field representation in patients with post-stroke hemianopia. *J. Neurol.* 257, 1832–1840. doi: 10.1007/s00415-010-5617-1

O'Neill, E. C., Connell, P. P., O'Connor, J. C., Brady, J., Reid, I., and Logan, P. (2011). Prism therapy and visual rehabilitation in homonymous visual field loss. *Optom. Vis. Sci.* 88, 263–268. doi: 10.1097/OPX.0b013e318205a3b8

Otero-Millan, J., Troncoso, X. G., Macknik, S. L., Serrano-Pedraza, I., and Martinez-Conde, S. (2008). Saccades and microsaccades during visual fixation, exploration and search: foundations for a common saccadic generator. *J. Vis.* 8:21. doi: 10.1167/8.14.21

Pambakian, A., Currie, J., and Kennard, C. (2005). Rehabilitation strategies for patients with homonymous visual field defects. *J. Neuroophthalmol.* 25, 136–142.

Pambakian, A. L., Mannan, S. K., Hodgson, T. L., and Kennard, C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. *J. Neurol. Neurosurg. Psychiatry* 75, 1443–1448. doi: 10.1136/jnnp.2003.025957

Pambakian, A. L. M., Wooding, D. S., Patel, N., Morland, A. B., Kennard, C., and Mannan, S. K. (2000). Scanning the visual world: a study of patients with homonymous hemianopia. *J. Neurol. Neurosurg. Psychiatry* 69, 751–759. doi: 10.1136/jnnp.69.6.751

Papageorgiou, E., Hardiess, G., Mallot, H. A., and Schiefer, U. (2012). Gaze patterns predicting successful collision avoidance in patients with homonymous visual field defects. *Vision Res.* 65, 25–37. doi: 10.1016/j.visres.2012.06.004

Passamonti, C., Bertini, B., and Làdavas, E. (2009). Audio-visual stimulation improves oculomotor patterns in patients with hemianopia. *Neuropsychologia* 47, 546–555. doi: 10.1016/j.neuropsychologia.2008.10.008

Pelak, V. S., Dubin, M., and Whitney, E. (2007). Homonymous hemianopia: a critical analysis of optical devices, compensatory training and novavision. *Curr. Treat. Options Neurol.* 9, 41–47. doi: 10.1007/s11940-007-0029-y

Plow, E. B., Obretenova, S. N., Fregni, F., Pascual-Leone, A., and Merabet, L. B. (2012). Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical stimulation. *Neurorehabil. Neural Repair* 28, 616–626. doi: 10.1177/1545968311431963

Poggel, D. A., Mueller, I., Kasten, E., Bunzenthal, U., and Sabel, B. A. (2010). Subjective and objective outcome measures of computer-based vision restoration training. *NeuroRehabilitation* 27, 173–187. doi: 10.3233/NRE-2010-0594

Poggel, D. A., Kasten, E., Müller-Oehring, E. M., Bunzenthal, U., and Sabel, B. A. (2006). Improving residual vision by attentional cueing in patients with brain lesions. *Brain Res.* 1097, 142–148. doi: 10.1016/j.brainres.2006.04.011

Poggel, D. A., Kasten, E., Müller-Oehring, E. M., Sabel, B. A., and Brandt, S. A. (2001). Unusual spontaneous and training induced visual field recovery in a patient with a gunshot lesion. *J. Neurol. Neurosurg. Psychiatry* 70, 236–239. doi: 10.1136/jnnp.70.2.236

Poggel, D. A., Kasten, E., and Sabel, B. A. (2004). Attentional cueing improves vision restoration therapy in patients with visual field defects. *Neurology* 63, 2069–2076. doi: 10.1212/01.wnl.0000145773.26378.e5

Poggel, D. A., Treutwein, B., and Strasburger, H. (2011). Time will tell: deficits of temporal information processing in patients with visual field loss. *Brain Res.* 1368, 196–207. doi: 10.1016/j.brainres.2010.10.065

Reinhard, J., Schreiber, A., Schiefer, U., Kasten, E., Sabel, B. A., Kenkel, S., et al. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *Br. J. Ophthalmol.* 89, 30–35. doi: 10.1136/bjo.2003.040543

Robertson, I. H., and Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol. Bull.* 125, 544–575. doi: 10.1037/0033-2909.125.5.544

Rolfs, M. (2009). Microsaccades: small steps on a long way. *Vision Res.* 49, 2415–2441. doi: 10.1016/j.visres.2009.08.010

Romano, J. G., Schulz, P., Kenkel, S., and Todd, D. P. (2008). Visual field changes after a rehabilitation intervention: vision restoration therapy. *J. Neurol. Sci.* 273, 70–74. doi: 10.1016/j.jns.2008.06.026

Rossi, P. W., Kheyfets, S., and Reding, M. J. (1990). Fresnel prisms improve visual perception in stroke patients with homonymous hemianopia or unilateral visual neglect. *Neurology* 40, 1597–1599. doi: 10.1212/wnl.40.10.1597

Roth, T., Sokolov, A. N., Messias, A., Roth, P., Weller, M., and Trauzettel-Klosinski, S. (2009). Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study. *Neurology* 72, 324–331. doi: 10.1212/01.wnl.0000341276.65721.f2

Sabel, B. A., and Gudlin, J. (2014). Vision restoration training for glaucoma: a randomized clinical trial. *JAMA Ophthalmol.* 132, 381–389. doi: 10.1001/jamaophthalmol.2013.7963

Sabel, B. A., Fedorov, A. B., Naue, N., Borrmann, A., Herrmann, C., and Gall, C. (2011a). Non-invasive alternating current stimulation improves vision in optic neuropathy. *Restor. Neurol. Neurosci.* 29, 493–505. doi: 10.3233/RNN-2011-0624

Sabel, B. A., Henrich-Noack, P., Fedorov, A., and Gall, C. (2011b). Vision restoration after brain and retina damage: the "residual vision activation theory". *Prog. Brain Res.* 192, 199–262. doi: 10.1016/b978-0-444-53355-5.00013-0

Sabel, B. A., Kenkel, S., and Kasten, E. (2004). Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires. *Restor. Neurol. Neurosci.* 22, 399–420.

Sabel, B. A., and Trauzettel-Klosinksi, S. (2005). Improving vision in a patient with homonymous hemianopia. *J. Neuroophthalmol.* 25, 143–149. doi: 10.1097/01.wno.0000165107.24108.49

Sahraie, A., Trevethan, C. T., MacLeod, M. J., Murray, A. D., Olson, J. A., and Weiskrantz, L. (2006). Increased sensitivity after repeated stimulation of residual spatial channels in blindsight. *Proc. Natl. Acad. Sci. U S A* 103, 14971–14976. doi: 10.1073/pnas.0607073103

Sautter, J., and Sabel, B. A. (1993). Recovery of brightness discrimination in adult rats despite progressive loss of retrogradely labelled retinal ganglion cells after controlled optic nerve crush. *Eur. J. Neurosci.* 5, 680–690. doi: 10.1111/j.1460-9568.1993.tb00533.x

Schadow, J., Dettler, N., Paramei, G. V., Lenz, D., Fründ, I., Sabel, B. A., et al. (2009). Impairments of Gestalt perception in the intact hemifield of hemianopic patients are reflected in gamma-band EEG activity. *Neuropsychologia* 47, 556–568. doi: 10.1016/j.neuropsychologia.2008.10.012

Schlack, A., Hoffmann, K. P., and Bremmer, F. (2002). Interaction of linear vestibular and visual stimulation in the macaque ventral intraparietal area (VIP). *Eur. J. Neurosci.* 16, 1877–1886. doi: 10.1046/j.1460-9568.2002.02251.x

Schmidt, S., Mante, A., Rönnefarth, M., Fleischmann, R., Gall, C., and Brandt, S. A. (2013). Progressive enhancement of alpha activity and visual function in patients with optic neuropathy: a two-week repeated session alternating current stimulation study. *Brain Stimul.* 6, 87–93. doi: 10.1016/j.brs.2012.03.008

Schofield, T. M., and Leff, A. P. (2009). Rehabilitation of hemianopia. *Curr. Opin. Neurol.* 22, 36–40. doi: 10.1097/WCO.0b013e32831f1b2c

Schuett, S., and Zihl, J. (2013). Does age matter? Age and rehabilitation of visual field disorders after brain injury. *Cortex* 49, 1001–1012. doi: 10.1016/j.cortex.2012.04.008

Serino, A., Cecere, R., Dundon, N., Bertini, C., Castaneda, S., and Làdavas, E. (2014). When apperceptive agnosia is explained by a deficit of primary visual processing. *Cortex* 52, 12–27. doi: 10.1016/j.cortex.2013.12.011

Shams, L., and Kim, R. (2012). "Crossmodal facilitation of unisensory learning," in *The New Handbook of Multisensory Processes*, ed. B. E. Stein (Cambridge, MA: The MIT Press), 475–482.

Stein, B. E., and Meredith, M. A. (1993). *Merging of the Senses.* Cambridge, MA: MIT Press.

Stein, B. E., and Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nat. Rev. Neurosci.* 9, 255–266. doi: 10.1038/nrn2377

Tamietto, M., Pullens, P., de Gelder, B., Weiskrantz, L., and Goebel, R. (2012). Subcortical connections to human amygdala and changes following destruction of the visual cortex. *Curr. Biol.* 22, 1449–1455. doi: 10.1016/j.cub.2012.06.006

Targher, S., Occelli, V., and Zampini, M. (2012). Audiovisual integration in low vision individuals. *Neuropsychologia* 50, 576–582. doi: 10.1016/j.neuropsychologia.2011.10.021

Trauzettel-Klosinski, S. (2011). Current methods of visual rehabilitation. *Dtsch. Arztebl. Int.* 108, 871–878. doi: 10.3238/arztebl.2011.0871

Troncoso, X. G., Macknik, S. L., and Martinez-Conde, S. (2008). Microsaccades counteract perceptual filling-in. *J. Vis.* 8:15. doi: 10.1167/8.14.15

Tsai, C. L., and Wang, W. L. (2015). Exercise-mode-related changes in task-switching performance in the elderly. *Front. Behav. Neurosci.* 9:56. doi: 10.3389/fnbeh.2015.00056

Vanni, S., Henriksson, L., Hyvärinen, L., Näsänen, R., and Raninen, A. (2010). Vision restoration through extrastriate stimulation in patients with visual field defects: a double-blind and randomized experimental study. Letter to the editor. *Neurorehabil. Neural Repair* 24, 204–206. doi: 10.1177/1545968309347684

Verlohr, D., and Dannheim, F. (2007). The visual performance test: indications for compensational visual rehabilitation training and first results. *Strabismus* 15, 63–68. doi: 10.1080/09273970601180305

Virgili, G., Acosta, R., Grover, L. L., Bentley, S. A., and Giacomelli, G. (2013). Reading aids for adults with low vision. *Cochrane Database Syst. Rev.* 10:CD003303. doi: 10.1002/14651858.CD003303

Webster, M. A. (2011). Adaptation and visual coding. *J. Vis.* 11:3. doi: 10.1167/11.5.3

Wiesel, T. N., and Hubel, D. H. (1965). Extent of recovery from the effects of visual deprivation in kittens. *J. Neurophysiol.* 28, 1060–1072.

Wu, J., Yan, T., Zhang, Z., Jin, F., and Guo, Q. (2012). Retinotopic mapping of the peripheral visual field to human visual cortex by functional magnetic resonance imaging. *Hum. Brain Mapp.* 33, 1727–1740. doi: 10.1002/hbm.21324

Zhang, X., Kedar, S., Lynn, M. J., Newman, N. J., and Biousse, V. (2006). Natural history of homonymous hemianopia. *Neurology* 66, 901–905. doi: 10.1212/01.wnl.0000203338.54323.22

Zihl, J. (1995). Visual scanning behavior in patients with homonymous hemianopia. *Neuropsychologia* 33, 287–303. doi: 10.1016/0028-3932(94)00119-a

Zihl, J. (1999). Oculomotor scanning performance in subjects with homonymous visual field disorders. *Vis. Impair. Res.* 1, 23–31. doi: 10.1076/vimr.1.1.23.4450

Zihl, J. (2000). *Rehabilitation of Visual Disorders After Brain Injury.* UK: Psychological Press.

Zihl, J. (2010). *Rehabilitation of Visual Disorders After Brain Injury.* 2nd Edn. New York: Psychology Press.

Zihl, J., and von Cramon, D. (1985). Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. *Brain* 108, 335–365. doi: 10.1093/brain/108.2.335

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

REVIEW
published: 11 September 2015
doi: 10.3389/fnbeh.2015.00234

Motor imagery reinforces brain compensation of reach-to-grasp movement after cervical spinal cord injury

Sébastien Mateo[1,2,3,4], Franck Di Rienzo[3], Vance Bergeron[4], Aymeric Guillot[3,5], Christian Collet[3] and Gilles Rode[1,2]*

[1] ImpAct Team, Lyon Neuroscience Research Center, Université Lyon 1, Université de Lyon, INSERM U1028, CNRS UMR5292, Lyon, France, [2] Hospices Civils de Lyon, Hôpital Henry Gabrielle, Plateforme Mouvement et Handicap, Lyon, France, [3] Centre de Recherche et d'Innovation sur le Sport, EA 647, Performance Motrice, Mentale et du Matériel, Université Lyon 1, Université de Lyon, Villeurbanne, France, [4] Ecole Normale Supérieure de Lyon, CNRS UMR5672, Lyon, France, [5] Institut Universitaire de France, Paris, France

Individuals with cervical spinal cord injury (SCI) that causes tetraplegia are challenged with dramatic sensorimotor deficits. However, certain rehabilitation techniques may significantly enhance their autonomy by restoring reach-to-grasp movements. Among others, evidence of motor imagery (MI) benefits for neurological rehabilitation of upper limb movements is growing. This literature review addresses MI effectiveness during reach-to-grasp rehabilitation after tetraplegia. Among articles from MEDLINE published between 1966 and 2015, we selected ten studies including 34 participants with C4 to C7 tetraplegia and 22 healthy controls published during the last 15 years. We found that MI of possible non-paralyzed movements improved reach-to-grasp performance by: (i) increasing both tenodesis grasp capabilities and muscle strength; (ii) decreasing movement time (MT), and trajectory variability; and (iii) reducing the abnormally increased brain activity. MI can also strengthen motor commands by potentiating recruitment and synchronization of motoneurons, which leads to improved recovery. These improvements reflect brain adaptations induced by MI. Furthermore, MI can be used to control brain-computer interfaces (BCI) that successfully restore grasp capabilities. These results highlight the growing interest for MI and its potential to recover functional grasping in individuals with tetraplegia, and motivate the need for further studies to substantiate it.

Keywords: tetraplegia, motor imagery, grasping, brain plasticity, motor control, kinematic, recovery, compensation

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Francoise Schenk, Université de Lausanne, Switzerland
Marco Iosa, Fondazione Santa Lucia, Italy

****Correspondence:***
Sébastien Mateo, Hospices Civils de Lyon, Hôpital Henry Gabrielle, Plateforme Mouvement et Handicap, 20 route de Vourles, F-69230 Saint Genis-Laval, Lyon, France
sebastien.mateo@chu-lyon.fr

Received: *18 May 2015*
Accepted: *19 August 2015*
Published: *11 September 2015*

Citation:
Mateo S, Di Rienzo F, Bergeron V, Guillot A, Collet C and Rode G (2015) Motor imagery reinforces brain compensation of reach-to-grasp movement after cervical spinal cord injury. Front. Behav. Neurosci. 9:234. doi: 10.3389/fnbeh.2015.00234

Introduction

Individuals with tetraplegia are challenged with dramatic sensorimotor deficits caused by cervical spinal cord injury (SCI). Active grasp is lost due to hand and finger muscle paralysis although compensation is possible (Long and Lawton, 1955; Kirshblum et al., 2007). Compensations are restricted to bimanual grasp after C5 SCI while other grips using the mouth or tongue compensate for grasp after C4 SCI. Tenodesis grasp relies on the spared wrist extensor muscle after C6 and C7 SCI. Indeed, tendon shortening of either the *flexor digitorum* or *flexor pollicis longus* occurs simultaneously to wrist extension resulting respectively in passive palmar or lateral grip (Mateo et al., 2013). These upper limb movement modifications are accompanied by increased activity of contralateral sensorimotor cortex, supplementary motor area and ipsilateral cerebellum, varying according to the SCI level (Bruehlmeier et al., 1998; Curt et al., 2002; Cramer et al., 2005; Jurkiewicz et al., 2007; Kokotilo et al., 2009). Improving grasping abilities are important issues for recovering autonomy of individuals with tetraplegia (Long and Lawton, 1955; Beninato et al., 2004). Consequently, rehabilitation aims to restore reach-to-grasp using physical and occupational therapies (Woolsey, 1985; Kirshblum et al., 2007).

There is growing evidence of motor imagery (MI) benefits for neurological rehabilitation of upper limb movements (Warner and McNeill, 1988; Jackson et al., 2001). The mental representation of an action without any physical execution engages brain motor regions overlapping those activated by physical practice (PP; Decety and Grèzes, 1999; Pfurtscheller, 2001). This functional equivalence principle was early described in healthy individuals (Jeannerod, 1994; Lotze and Halsband, 2006; Hanakawa et al., 2008; Munzert et al., 2009) and in individuals with SCI (Decety and Boisson, 1990; Lotze and Halsband, 2006; Di Rienzo et al., 2014a). Thus MI enables active stimulation of brain motor areas promoting brain plasticity (Lotze and Halsband, 2006; Dunlop, 2008) associated with positive effects on motor performance (Driskell et al., 1994).

Thereby, MI could constitute a promising approach to rehabilitate grasping abilities after C6 and C7 tetraplegia. Furthermore, individuals with C4 and C5 tetraplegia could imagine movements to control a device that can replace grasping using brain-computer interfaces (BCI; Pfurtscheller et al., 2003a). BCI extract the somato-topically organized sensorimotor rhythms from brain activity during MI (Yuan and He, 2014). The BCI then transforms brain activity into signals driving an output to control a grasping device. A BCI requires several steps including: (i) preprocessing to improve signal-to-noise ratio; (ii) frequency selection where the greatest amplitude of sensorimotor rhythms during MI are measured; and (iii) detection and classification where participants are extensively trained to imagine a movement with or without cues, which results in a less adaptive synchronous BCI (cue-paced) or a more adaptive asynchronous BCI (self-paced).

The aim of this literature review is to address the effectiveness of MI upon upper limb rehabilitation after tetraplegia. More precisely, we will investigate behavioral changes (reduction of upper limb functional deficit) and brain activity changes in response to MI intervention. Understanding the potential for MI to improve motor performance by reinforcing compensations or potentiating recovery, with or without influence on brain plasticity is of particular interest.

Materials and Methods

We selected full articles from the U.S. National Library of Medicine® (MEDLINE) between 1966 and June 2015 assessing the effect of MI intervention in individuals with complete motor tetraplegia. Included are single case, case series and control case studies of MI intervention on upper limb and tongue trials with pre-post movement performance or brain activity recordings. Excluded studies are those without grasping deficit e.g., in individuals with paraplegia, without complete SCI, and/or when MI intervention only involved lower limb movements. We analyzed behavioral improvement due to MI intervention on several dependent variables (performance, velocity, manual dexterity and kinematics) while also considering brain activity changes in response to MI.

Results

Studies

Figure 1 provides a flowchart that illustrates and summarizes the literature review process we used. From the 306 articles screened, papers that did not fulfill at least one of our exclusion criteria were not considered. This resulted in exclusion of 230 articles after reading the title and/or abstract. Among the 76 remaining full-text articles, 66 papers were rejected for the following reasons:

1. MI studies with no tetraplegic participants (Boschker et al., 2000; Pfurtscheller et al., 2003b; Wilson, 2003; Erfani and Erfanian, 2004; Erfanian and Erfani, 2004; Grush, 2004; Grosjean et al., 2007; Szpunar et al., 2007; Miller et al., 2010; Müller-Putz et al., 2010; Olsson and Nyberg, 2010; Schill et al., 2011; Viswanathan et al., 2012; Papageorgiou et al., 2013; Smits-Engelsman and Wilson, 2013; Kondo et al., 2014; Grosprêtre et al., 2015; Malik et al., 2015);
2. Studies including tetraplegic participants with no MI intervention (Saxena et al., 1995; de Castro and Cliquet, 2000a,b; Laffont et al., 2000, 2007, 2009; Memberg and Crago, 2000; Thorsen et al., 2001, 2014; Hoffmann et al., 2002; Nunome et al., 2002; Taylor et al., 2002; Remy-Neris et al., 2003; Shimada et al., 2003; Cornwall and Hausman, 2004; Pfurtscheller et al., 2005; Anderson et al., 2008; Robinson et al., 2010; de los Reyes-Guzmán et al., 2010; Martin et al., 2012; Siedziewski et al., 2012; Coignard et al., 2013; Collinger et al., 2013a,b; Cortes et al., 2013; Mateo et al., 2013, 2015a; Wodlinger et al., 2015);
3. MI of lower limb movements only (Pfurtscheller et al., 2008; Flanagin et al., 2009; Tcheang et al., 2011);
4. Articles without pre-post measures (Decety and Boisson, 1990; Lacourse, 1999; An et al., 2006; De Mauro et al., 2011; Ajiboye et al., 2012; Blokland et al., 2012, 2014; Grangeon et al., 2012b; López-Larraz et al., 2012; Fiori et al., 2014; Müller-Putz et al., 2014); and
5. Articles without movement performance assessment (Enzinger et al., 2008; Di Rienzo et al., 2014b, 2015; Faller et al., 2014; Scherer et al., 2015; Tidoni et al., 2015).

We thus included 10 studies involving five single case (Pfurtscheller et al., 2000; Müller-Putz et al., 2005; Grangeon et al., 2010, 2012a; Rohm et al., 2013), two case series (Onose et al., 2012; Vučković et al., 2015) and three control cases (Cramer et al., 2007; Di Rienzo et al., 2014c; Mateo et al., 2015b). We scored the quality of these studies using the Single-Case

Experimental Design (SCED) scale (Tate et al., 2008), the 3 min critical appraisal for case series (Chan and Bhandari, 2011) and the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003; de Morton, 2009). The SCED scores were 5/10 (Grangeon et al., 2010, 2012a) and 3/10 (Pfurtscheller et al., 2000; Müller-Putz et al., 2005; Rohm et al., 2013). The absence of a baseline and statistical analysis explained the difference in score. Similarly, the control case series studies all had a 5/10 PEDro score. We note that PEDro scores below 6/10, have been considered as low quality (Paci et al., 2010). Only the two case series studies were evaluated as having so-called high quality (Chan and Bhandari, 2011).

Participants

The 10 studies involved a total of 34 participants with tetraplegia and 22 healthy age-matched controls. Mean age was 33 years (22–42). SCI Levels were C4 (n = 3), C5 (n = 9), C6 (n = 16) and C7 (n = 6; see **Table 1**). All participants were at a chronic stage (mean = 31 months after SCI 3.5–84) with the exception of two who were included 3 and 4 months after SCI (Vučković et al., 2015). Furthermore, all studies included participants with complete motor lesion AIS A or B, except the article by Onose et al. (2012), which included two participants with AIS C. MI vividness was on average self-rated at 3.6/5 (from 3.3–4.1) and 3.3/5 (from 2.2–3.8) for visual and kinesthetic MI modalities, respectively (Grangeon et al., 2012a; Di Rienzo et al., 2014c; Mateo et al., 2015b; Vučković et al., 2015).

Outcome Measures

MI intervention effects were assessed through clinical and kinematic outcomes, along with changes in brain activity. These include: (i) passive range of motion measured with a goniometer (Grangeon et al., 2010); (ii) muscle strength assessed by the Manual Muscle Test (Grangeon et al., 2010; Vučković et al., 2015); (iii) manual dexterity outcome using the Minnesota Manual Dexterity Test (MMDT), the Block and Box Test (BBT; Grangeon et al., 2012a) and the Grasp and Release Test (GRT; Müller-Putz et al., 2005); and (iv) kinematic outcomes during reaching and reach-to-grasp movements including temporal parameters e.g., movement time (MT) and spatial parameters e.g., trajectory, joint motion, wrist extension angle during grasping (Grangeon et al., 2010, 2012a; Mateo et al., 2015b). In addition, outcomes of grasping effectiveness have also been done using a BCI device controlled by MI (Pfurtscheller et al., 2000; Müller-Putz et al., 2005; Onose et al., 2012; Rohm et al., 2013; Vučković et al., 2015). Finally, 8 studies investigated brain activity changes in response to MI using electroencephalography (EEG; Pfurtscheller et al., 2000; Müller-Putz et al., 2005; Onose et al., 2012; Rohm et al., 2013; Vučković et al., 2015), functional magnetic resonance imaging (fMRI; Cramer et al., 2007) or magnetoencephalagraphy (MEG; Di Rienzo et al., 2014c; Mateo et al., 2015b).

MI Interventions

Mean data showed that participants rehearsed mentally during 598 min (range from 300–900). However, one study did not report MI practice duration (Rohm et al., 2013; **Table 1**). Instead, Rohm et al. (2013) indicated that participants performed 413 MI trials. The mean number of MI sessions was 14 (range from 3–43) over 10 weeks (range from 0.4–52). Practice before MI consisted of video observation (Cramer et al., 2007; Onose et al., 2012) or PP with a crossover design (Grangeon et al., 2010) and without crossover (Grangeon et al., 2012a; Di Rienzo et al., 2014c; Mateo et al., 2015b). Conversely, there was no practice before MI in the other studies (Pfurtscheller et al., 2000; Müller-Putz et al., 2005; Cramer et al., 2007; Rohm et al., 2013; Vučković et al., 2015). SCI participants imagined single-joint movements of: (i) wrist flexion/extension (Di Rienzo et al., 2014c; Mateo et al., 2015b); (ii) hand movements (Müller-Putz et al., 2005; Rohm et al., 2013); (iii) arrhythmic flexion/extension of both finger and ankle (Onose et al., 2012); or (iv) functional movement of reaching and reach-to-grasp (Grangeon et al., 2010, 2012a; Di Rienzo et al., 2014a; Mateo et al., 2015b).

In cases of C4-C5 SCI, grasping was achieved using MI based BCI via an EEG to control a motorized hand orthosis (Pfurtscheller et al., 2000), an implanted functional electrical stimulation (FES; Müller-Putz et al., 2005), a surface FES (Rohm et al., 2013; Vučković et al., 2015) or a grasping robot (Onose et al., 2012). The EEG recorded the electrical activity over the sensorimotor cortex (electrodes were located at C3, Cz and C4 according to the 10–20 international system). Then, the frequency range showing the highest sensorimotor rhythms within the alpha/mu and beta bands (8–13, 13–35 Hz) were tailored to each participant. All but one study used two imagined movements to generate the output signal and control the device, with the exception of Müller-Putz et al. (2005) who only used one imagined movement to control the device. The total amount of MI training ranged between 3 and 1012 sessions (see **Table 2**). The ratio between correctly classified trials and the total number of trials (i.e., the classification accuracy; Graimann et al., 2010) ranged between 71 and 95%. Finally, SCI participants controlled the device to restore grasping using either self-paced MI i.e., asynchronous BCI (Müller-Putz et al., 2005; Vučković et al., 2015) or cue-paced MI i.e., synchronous BCI (Pfurtscheller et al., 2000; Onose et al., 2012; Vučković et al., 2015).

Clinical Evidence of MI Effectiveness

Using a crossover design, Grangeon et al. (2010) reported motor improvement whatever the order of practice (PP before MI or after). The chronic C6 SCI participants exhibited; (i) increased amplitude of passive elbow flexion (from 90° to 145°), and (ii) increase in strength of both the elbow flexor and extensor muscles respectively from 2 to 4/5 and 1 to 4/5 on the Manual Muscle Testing score, indicating that the movement could subsequently be performed against gravity and even against a light resistance after MI training. Similarly, after training of triggered electrical stimulation using MI-based BCI, Vučković et al. (2015) showed that one of the two C5 acute SCI participants increased *brachioradialis* strength (from 1 to 3/5, i.e., the initial palpable muscle

TABLE 1 | Participants and studies characteristics.

Reference	Study	SCI level	Patient	AIS Score (A–E)	Mean age (years)	Mean delay (months)	MI				Outcome	
							Training before MI	Sessions	Duration (min)	Content	Behavioral activity	Brain
Pfurtscheller et al. (2000)	SC	C5	1	NA	22	24	No	NA	NA	Hand foot	Grasping*	EEG
Müller-Putz et al. (2005)	SC	C5	1	A	42	84	No	3	540	Hand foot	Grasping*	EEG
Cramer et al. (2007)	CC	C5 C6	5 1[a]	A, B	30 *(SD 4)*	Up to 12	Observation[c]	7	420	Tongue foot	Movement frequency	fMRI
Grangeon et al. (2010)	SC	C6	1	A	41	32	PP[d]	20	300	Reaching grasping	Strength reaching**	NA
Grangeon et al. (2012a)	SC	C6	1	A	23	8	PP	15	675	Reaching grasping	Dexterity*** Grasping**	NA
Onose et al. (2012)	CS	C4 C6 C7	2 3 4	A, B, C	33 *(23–51)*	66 *(6–202)*	Observation[c]	5	900	Hand ankle	Grasping*	EEG
Rohm et al. (2013)	SC	C4	1	A	42	48	No	43	NA	Hand	Grasping*	EEG
Di Rienzo et al. (2015)[e]	CC	C6 C7	5 1[b]	A, B	30 *(18–40)*	14 *(6–30)*	PP	15	675	Reaching grasping	Movement duration	MEG
Vučković et al. (2015)	CS	C5	2	A, B	39 *(32–45)*	3.5 *(3–4)*	No	4–10	NA	Hand	Grasping*	EEG
Mateo et al. (2015b)[e]	CC	C6 C7	5 1	A, B	30 *(18–40)*	14 *(6–30)*	PP	15	675	Reaching grasping	Grasping**	MEG

*Abbreviations: NA, Not Available; SC, single case; CS, case series; CC, control case; C, cervical level of SCI; MI, Motor Imagery; PP, Physical Practice; EEG, Electroencephalography; fMRI, functional Magnetic Resonance Imaging; MEG, Magnetoencephalography. Number of control participants included was [a]10, [b]6, [c]observation of video showing the movement to perform, [d]crossover design with PP before MI and after, [e]Both references are from the same scientific team and included the same group of participants with tetraplegia. *Grasping was achieved with MI based BCI controlling a grasping device, **kinematic of a reaching or reach-to-grasp task, ***dexterity was assessed using the Block and Box Test and the Minnesota Manual Dexterity Test.*

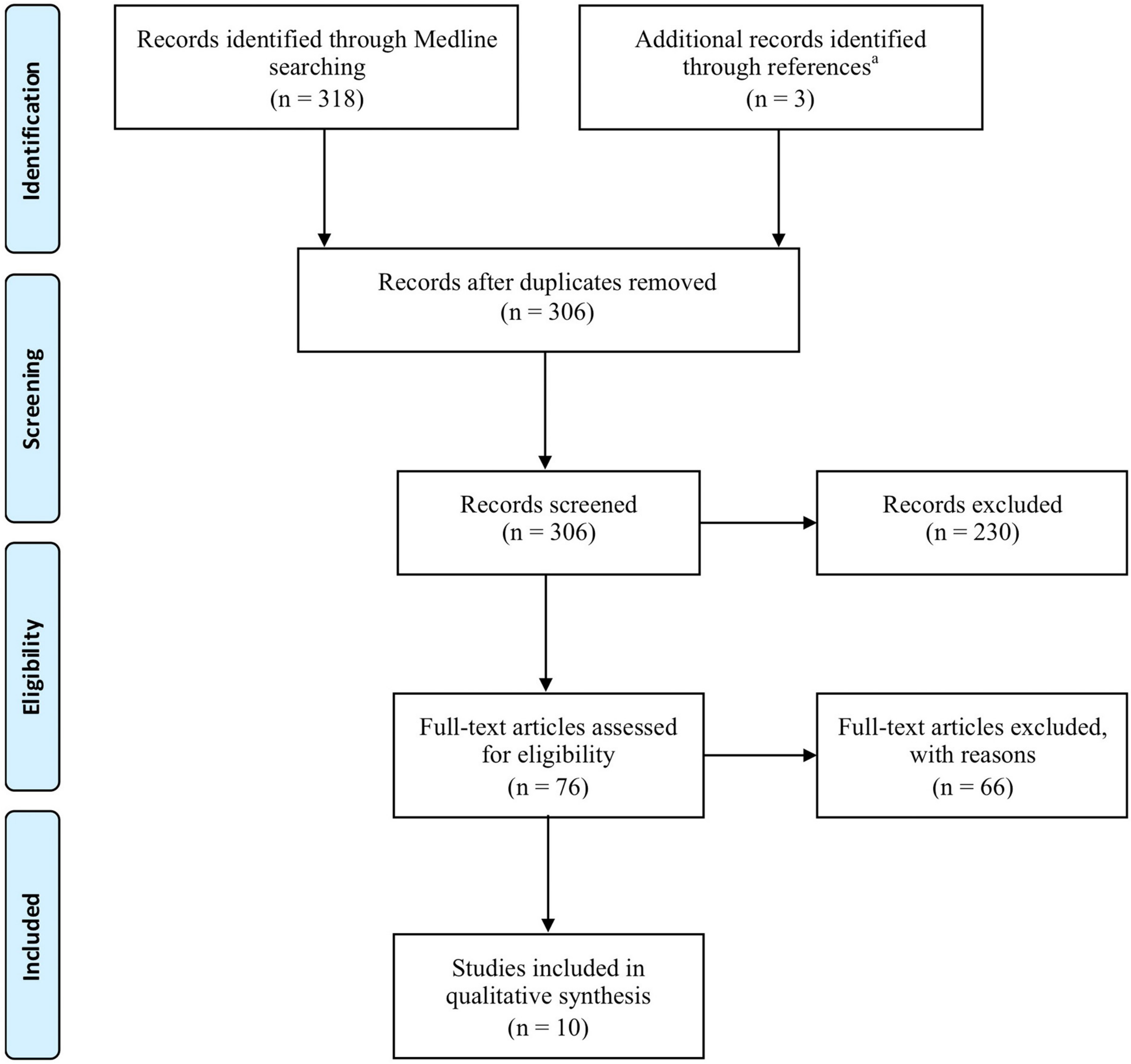


FIGURE 1 | Flow diagram of review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA—Moher et al., 2009). [a]The three identified papers were (Laffont et al., 2000; Hoffmann et al., 2002; Collinger et al., 2013b).

contraction changed to full elbow flexion range of motion against gravity).

In response to MI of possible upper limb movements (e.g., grasping), one C6 SCI participant demonstrated increased manual dexterity as shown by; (i) significant improvement in the BBT; and (ii) decreased time to complete the MMDT (Grangeon et al., 2012a). Similarly, six C6-C7 SCI participants showed decreased variability of MTs during a complete reach-to-grasp sequence, including bringing an apple to the mouth and then putting it back in its initial location (Di Rienzo et al., 2014c). In addition, after learning a movement sequence using MI of either the right foot or the tongue, seven C5 to C7 SCI participants only exhibited a decreased in MT to complete the sequence with the tongue (i.e., during practice of possible movements; Cramer et al., 2007).

Furthermore, training of MI based BCI resulted in compensation of grasping movements with the successful control of the BCI device. By controlling surface FES, one C4 SCI participant showed decreased MT when grasping, along with writing his own name or eating an ice cream cone (Rohm et al., 2013). Similarly, one C5 SCI participant successfully grasped a paperweight in the GRT and moved it five times from one place to another (Müller-Putz et al., 2005). By controlling a motorized hand orthosis, another C5 SCI participant grasped and ate an apple (Pfurtscheller et al., 2000). In addition, by controlling an upper limb robot 3 of 9 C5 SCI participants successfully grasped a glass and drank from it (Onose et al., 2012; **Table 2**).

TABLE 2 | MI Based BCI efficacy studies to compensate grasping function.

Reference	Patient	BCI type	Frequency (Hz)	MI Detection (cue)	Class	MI	Classifier	Maximum of sessions	Classification accuracy[1]	Device controlled	BCI output
Pfurtscheller et al. (2000)	1	S	15–18	Auditory	2	R, F	LDA[2]	NA	95%[3]	Orthosis	F: orthosis opening R: orthosis closing
Müller-Putz et al. (2005)	1	A	14–16 18–22	No	1	L, F	LDA[2]	3	73%	I FES[4]	L: FES sequence start[5]
Onose et al. (2012)	9	S	13–30	Visual	2	L, R, F, N	LDA[2]	10	71%	Robot[6]	Two classes for robot start and stop[7]
Rohm et al. (2013)	1	S	23–26	Visual	2	R, F	LDA[2]	119	71%	S FES[8]	R: BCI switch[9]
Vučković et al. (2015)	2	S	4–8 12–16	Visual	2	R, F	NA	1012	85%	S FES[10]	R: FES start E: FES stop

Abbreviations: BCI, Brain-computer interface; MI, Motor Imagery; S, synchronous; A, Asynchronous; R, Right hand; L, Left hand; E, Eye closing; F, Feet; N, No movement i.e., relaxation; NA, Not Available; I, Implanted; S, Surface; FES, Functional Electrical Stimulation. [1]Is a BCI measure of performance given by a ratio of the number of correctly classified trials (successful attempts to perform the required MI) and the total number of trials (Graimann et al., 2010), [2]Linear Discriminant Analysis is a linear classifier categorizing MI in several classes that can be affected to different function, [3]Accuracy was 65% when participant imagined L vs. R, improved to 75% when he imagined movement of L/R or F vs. N and finally improved to 95% when he imagined R vs. F, [4]The implanted FES was the freehand® system, [5]The three-part sequence of FES consisted in (i) finger extension (including thumb), (ii) finger flexion triggering palmar grip and (iii) thumb flexion triggering lateral grip, [6]Upper limb robot with 10 degrees of freedom, [7]Depending on participants, the pair for robot start stop was respectively L/N (n = 2), L/F (n = 3), F/N (n = 1), L/R (n = 4), [8]Surface FES restored elbow flexion and grasping with palmar grip, [9]Four BCI switch producing the sequence of (i) elbow extension then, (ii) grasping then, (iii) elbow flexion to eat then, (iv) elbow extension and hand opening to release the object, [10]Surface FES elicited stimulation of the wrist extensor carpi radialis longus using stimulation parameters set with pulse of 300 μs duration, 15 mA amplitude and 30 Hz frequency.

Kinematic Evidence of MI Effectiveness

Variability of hand trajectory decreased during reaching toward a central target placed 15 cm from a starting point in one C6 SCI participant (Grangeon et al., 2010). Similarly, variability of hand trajectory decreased by 58% during reach-to-grasp of a glass placed 40 cm in the front of the C6 SCI participant (Grangeon et al., 2012a; **Figure 2**). In addition, MT decreased by about 29% (Grangeon et al., 2012a). Finally, six C6-C7 SCI participants increased their wrist extension angle by 28% (i.e., wrist extension triggering tenodesis grasp) during reach-to-grasp of an apple placed at 35 cm (Mateo et al., 2015b). Motor improvements were preserved during retention tests, up to 2 months (Mateo et al., 2015b) and 3 months (Grangeon et al., 2012a) after MI training was stopped.

Brain Activity Modification in Response to MI

In response to MI of impossible paralyzed movements (e.g., foot), seven C5 to C7 SCI participants showed increased activation in the left putamen and globus pallidus during imagined foot movements measured by fMRI (Cramer et al., 2007). Similarly, one C5 SCI participant performing foot-movement MI exhibited increased amplitude of EEG sensorimotor rhythms in the cortical areas controlling the foot (Pfurtscheller et al., 2000). Conversely, MI practice of possible movements spared from SCI (e.g., reach-to-grasp) resulted in a decrease in the left premotor cortex activity during complete reach-to-grasp with the right hand in six C6-C7 SCI participants measured by MEG (Di Rienzo et al., 2014c). Similarly, six C6-C7 SCI participants exhibited decreased contralateral sensorimotor activity measured by MEG during wrist-extension triggering of the tenodesis grasp (Mateo et al., 2015b; **Figure 3**).

Discussion

The interest of using MI practice during upper limb rehabilitation after tetraplegia is growing. The effectiveness of MI to promote upper limb rehabilitation after tetraplegia remains nevertheless poorly understood. The aim of this review is to address the extent to which MI practice of possible movements spared from cervical SCI or impossible paralyzed movements may activate and reinforce cerebral networks in order to promote recovery or reinforce compensation during rehabilitation of reach-to-grasp movement after tetraplegia.

The training effects of MI on possible movement recovery have been studied through strength assessments using the Manual Muscle Test (Compston, 2010). Indeed, one chronic C6 SCI participant underwent surgical tendon transfer of the *biceps brachii* onto that of the *triceps brachii* and exhibited strength increase in both elbow flexor and extensor muscles in response to 2 weeks of MI practice (Grangeon et al., 2010). Here, improvement in strength relies on central modifications favoring: (i) change in *biceps brachii* function from elbow flexion to extension; and (ii) compensation of the loss of the transferred *biceps brachii* by the two remaining elbow flexor muscles (*brachioradialis and brachialis*). Moreover, strength increase was reported in the *brachioradialis* of one acute C5 SCI participant after seven MI sessions of

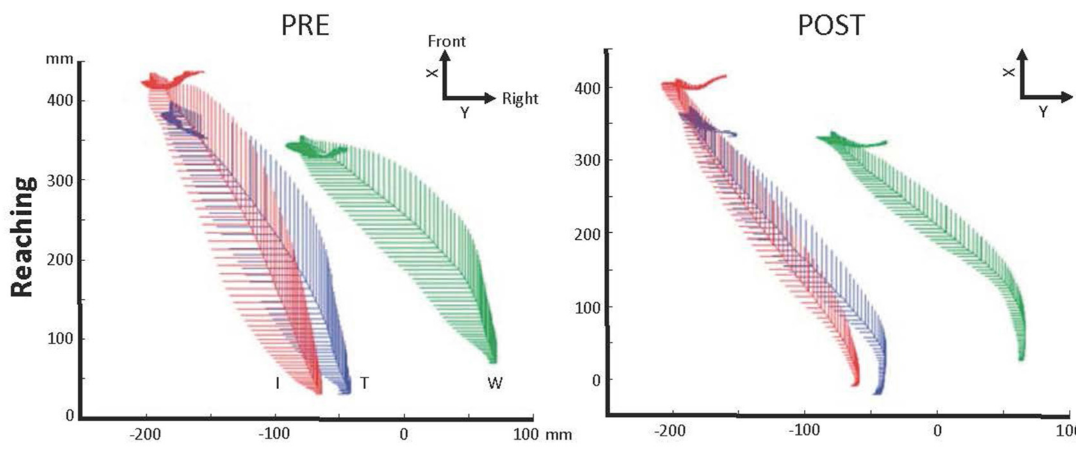


FIGURE 2 | Illustration of the motor control improvement after motor imagery (MI) practice in one C6 SCI participant. Kinematic recordings showing trajectory variability decrease of the right index finger (I—red), thumb (T—blue) and wrist (W—green) during reaching in the contralateral space immediately after MI practice, 1 and 3 months later (POST; adapted with permission from Grangeon et al., 2012a). Abbreviations: X, X-axis sets in participant's frontal plane; Y, Y-axis sets in participant's sagittal plane.

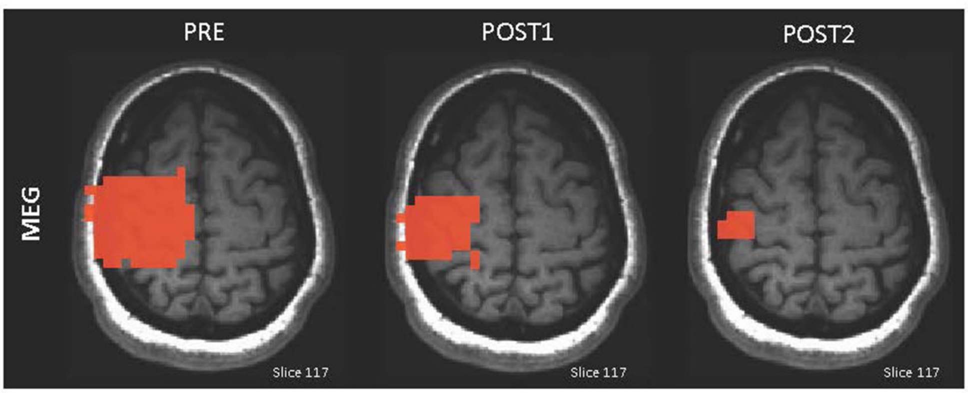


FIGURE 3 | Illustration of the adaptive brain plasticity after MI practice in one C6 SCI participant. Magnetoencephalography (MEG) maps displaying the contralateral sensorimotor activation decrease immediately after MI training (POST1) and 2 months later (POST2; adapted with permission from Mateo et al., 2015b).

grip preparation aimed at restoring grasp using surface FES controlled by BCI (Vučković et al., 2015). This is consistent with a similar strength increase in the little finger abductor and elbow flexor muscles reported in response to MI in healthy individuals (Yue and Cole, 1992; Ranganathan et al., 2004). Associated with these gains, EEG showed that the amplitude of sensorimotor rhythms increase during maximal voluntary contraction of the trained muscles, particularly during the power signal decrease i.e., the event related desynchronization (Ranganathan et al., 2004). From these observations, gain in strength has been attributed to central motor planning improvement, such as better recruiting and synchronizing of motoneurons in absence of muscle hypertrophy (Yue and Cole, 1992). Furthermore, based on EEG results, Ranganathan et al. (2004) concluded that MI "*enhances the cortical output signal, which drives the muscles to higher activation levels and increases strength*". Although these results should be associated with processes of natural recovery and rehabilitation, MI may have the potential to strengthen motor commands of upper limb movements, thus improving recovery.

Results from the other studies suggest a potential MI effect on compensation improvements during reach-to-grasp. One example is the BBT and MMDT improvements in response to 675 min of upper limb MI in a complete C6 SCI participant (Grangeon et al., 2012a). This may be related to the kinematic measures that reveal wrist extension increases, in the tenodesis grasp of six C6-C7 SCI participants, also after 675 min of MI practice (Mateo et al., 2015b). Taken together, the results suggest that hand dexterity improved which can be explained by endpoint movement accuracy and reinforcement of the tenodesis grasp. Thus, MI may have strengthened the motor planning (Mateo et al., 2015a). Furthermore, the reduction in hand trajectory variability indicates a reduction in both reaching and grasping movement inefficiencies (Grangeon et al., 2010, 2012a). Since reach-to-grasp is sub-divided into a transport phase (specifically tested by reaching) and a grasping phase (Jeannerod, 1984), overall motor control improvements involve both phases. This suggests that MI also reinforces the motor planning based on the kinematic invariant of minimal cost (Mateo et al., 2015a). Additionally, movement duration is also an index of performance. In response to MI of possible movements, duration of both reach-to-grasp and tongue sequence movements decrease (Cramer et al., 2007; Grangeon et al., 2012a) along with movement duration variability (Di Rienzo et al., 2014c). Hence, MI of possible movements is likely to: (i) promote the learning of new movement sequences; and (ii) improve the tenodesis grasp strategy that is one cause of MT reduction after tetraplegia (Mateo et al., 2015a). Therefore, these results imply that MI of possible movements reinforces strategies of movement planning according to kinematic invariants like minimal cost and endpoint movement accuracy (Mateo et al., 2015a). Here again, the effects of MI are thought to be limited to the central level by reinforcing the necessary motor commands and by building new motor commands through brain plasticity (Dunlop, 2008).

MI can induce brain plasticity through active stimulation of brain motor networks (Lotze and Halsband, 2006; Dunlop, 2008). Consequently, MI has been used to test if it can reduce the abnormally increased brain activity after tetraplegia (Kokotilo et al., 2009) using both impossible movements (e.g., foot) or possible movements (e.g., hand). After 420 min of MI training based on impossible foot movement sequences, Cramer et al. (2007) reported increased activity in the left putamen and globus pallidus. These areas are associated with motor learning and foot movements and can thus be considered as new movements that are not physically practiced due to paralysis. Consequently, this change in brain activity may relate to the first stage of motor learning (Karni et al., 1998). However, the absence of brain activity reduction in response to MI of impossible movement could not be definitively concluded because MI practice duration was short (7 days) and further practice could have resulted in the hypothesized brain activity changes (Doyon and Benali, 2005). Conversely, after 675 min of MI on possible upper limb movements, the additional recruitment in premotor cortex during grasping, compared to healthy control participants before MI training, was no longer observed (Di Rienzo et al., 2014c). In addition, the abnormally increased activity within the contralateral sensorimotor cortex during wrist-extension, was reduced and matched with healthy controls (Mateo et al., 2015b). Since both premotor- and sensorimotor cortex have been associated with motor planning during MI (Guillot et al., 2014), reduced activity could be due to "automation" thus involving cortical motor regions, parietal cortex, basal ganglia, and cerebellum (Doyon and Benali, 2005; Doyon et al., 2009; Vahdat et al., 2015). Along these lines, Cramer et al. (2007) reported that movement automation was associated with increased activity in basal ganglia even if C6 SCI participants performed MI of impossible foot movements. There is no additional evidence of brain activity changes within sub-cortical and cerebellar areas, related to MI learning after tetraplegia. However, considering functional equivalence between MI and PP, brain plasticity could be inferred from motor learning through actual practice. Hence, healthy participants exhibited activity decrease in the motor related brain areas involving cortico-basal ganglia and cortico-cerebellar pathways associated with more efficient skills requiring less energy (Doyon et al., 2009). Vahdat et al. (2015) recently investigated brain-spinal cord activity changes after actual training of finger movements. Healthy individuals showed that connectivity between sensorimotor cortex and the spinal cord decreased while that between cerebellum and the spinal cord was reinforced during learning. Whether these changes are less likely to occur after MI due to motor command inhibition remains unknown. Nevertheless, spinal cord plasticity induced by MI practice cannot be excluded since inhibition is weakened after SCI (Roy et al., 2011; Di Rienzo et al., 2014b) while corticospinal facilitation below motor threshold can occur (Stinear, 2010). Consequently, further studies should look for plasticity evolution in the motor related brain areas even considering the spinal cord after MI practice. Finally, the results we reviewed here, generally suggest that MI practice of possible and impossible movements resulted in a fundamental difference in brain plasticity. MI practice of impossible movements could be seen as learning a new task due to paralysis. Conversely, there is some evidence that increased activity caused by SCI is negated after MI training of possible movements. It is also noteworthy to mention that cortical changes, in particular after MI training of possible movements, could be associated with motor control and movement performance improvement due to the reinforcement of compensatory movement (e.g., tenodesis grasp).

Although there have been limited studies, promising evidence of MI based BCI efficacy to compensate for inability to grasp is also accumulating. Indeed, participants with C4 and C5 tetraplegia have gradually become able to control a grasping BCI device using extensive MI training of impossible movements (e.g., right, left hand or feet). In parallel, sensorimotor rhythms of imagined foot movements matched those from healthy control participants after 5 months of training (Pfurtscheller et al., 2000). This indicates that MI of impossible movements could restore brain activity reversing the reduction of sensorimotor rhythms which was previously reported during MI of impossible movements (Lacourse, 1999). As in healthy populations, MI has the ability to reinforce brain activity, leading to its use in controlling a BCI device. Nevertheless, the diversity of devices (e.g., surface or implanted FES, motorized hand orthosis or grasping robot) and methods (based on choice of frequency recorded or on type of movement imagined) or data processing (EEG data treatment leading to device control output) require further development to promote their routine use in rehabilitation. In particular, several issues should be further addressed e.g., the limited number of degrees of freedom controlled by MI based BCI, along with the reduction of MI training duration to control the device, from 5 months to 3 days respectively in the articles by Pfurtscheller et al. (2000) and Müller-Putz et al. (2005).

Conclusion

This literature review included 10 studies involving MI training for cervical SCI published over the last 15 years. The interest for using MI stems from its use as a complementary technique during grasping rehabilitation after tetraplegia. The results we briefly described here show motor control and performance improvement in response to MI of possible movements in individuals with SCI. This could be attributed to the improvement of compensation movements like the tenodesis grasp and to a lesser extend strength recovery. In addition, thus far it appears that only MI of possible movements can reduce abnormally increased brain activity as compared to control participants. Taken together, motor performance and brain plasticity reflect functional and structural changes in the central nervous system enabling the improvement of the compensated grasping movements. Furthermore, MI based BCI is a promising procedure which could further complete rehabilitation programs, in particular for the case of high level SCI (C4 and C5). Despite promising results and potential use of MI in rehabilitation methods, current studies provide only a weak level of evidence (Guyatt et al., 2008). Thus at this point, any generalization of results must be taken with caution and future studies should strive to eliminate potential bias due to low quality, and small sample sizes of SCI participants. Further investigations providing randomized controlled trials with a high evidence level are needed to confirm the MI effects for grasp rehabilitation after tetraplegia and to elucidate any changes in brain plasticity.

Author Contributions

SM, CC, GR made substantial contributions to the conception, acquisition, analysis and interpretation of data for the work. SM, FDR, VB, AG, CC, GR drafted the work and revised it critically for important intellectual content. All authors approved the final version to be published and acknowledged that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgment

Principal source of funding with Clinical Research Hospital Program 2010-541/142.

References

Ajiboye, A. B., Simeral, J. D., Donoghue, J. P., Hochberg, L. R., and Kirsch, R. F. (2012). Prediction of imagined single-joint movements in a person with high level tetraplegia. *IEEE Trans. Biomed. Eng.* 59, 2755–2765. doi: 10.1109/tbme.2012.2209882

An, B., Ning, Y., Jiang, Z., Feng, H., and Zhou, H. (2006). Classifying ECoG/EEG-based motor imagery tasks. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 1, 6339–6342. doi: 10.1109/iembs.2006.259567

Anderson, K., Aito, S., Atkins, M., Biering-Sørensen, F., Charlifue, S., Curt, A., et al. (2008). Functional recovery measures for spinal cord injury: an evidence-based review for clinical practice and research: report of the national institute on disability and rehabilitation research spinal cord injury measures meeting. *J. Spinal Cord Med.* 31, 133–144.

Beninato, M., O'Kane, K. S., and Sullivan, P. E. (2004). Relationship between motor FIM and muscle strength in lower cervical-level spinal cord injuries. *Spinal Cord* 42, 533–540. doi: 10.1038/sj.sc.3101635

Blokland, Y., Spyrou, L., Thijssen, D., Eijsvogels, T., Colier, W., Floor-Westerdijk, M., et al. (2014). Combined EEG-fNIRS decoding of motor attempt and imagery for brain switch control: an offline study in patients with tetraplegia. *IEEE Trans. Neural Syst. Rehabil. Eng.* 22, 222–229. doi: 10.1109/tnsre.2013.2292995

Blokland, Y., Vlek, R., Karaman, B., Özin, F., Thijssen, D., Eijsvogels, T., et al. (2012). Detection of event-related desynchronization during attempted and imagined movements in tetraplegics for brain switch control. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 3967–3969. doi: 10.1109/embc.2012.6346835

Boschker, M. S., Bakker, F. C., and Rietberg, M. B. (2000). Retroactive interference effects of mentally imagined movement speed. *J. Sports Sci.* 18, 593–603. doi: 10.1080/02640410050082305

Bruehlmeier, M., Dietz, V., Leenders, K. L., Roelcke, U., Missimer, J., and Curt, A. (1998). How does the human brain deal with a spinal cord injury? *Eur. J. Neurosci.* 10, 3918–3922. doi: 10.1046/j.1460-9568.1998.00454.x

Chan, K., and Bhandari, M. (2011). Three-minute critical appraisal of a case series article. *Indian J. Orthop.* 45, 103–104. doi: 10.4103/0019-5413.77126

Coignard, P., Departe, J. P., Remy Neris, O., Baillet, A., Bar, A., Drean, D., et al. (2013). ANSO study: evaluation in an indoor environment of a mobile assistance robotic grasping arm. *Ann. Phys. Rehabil. Med.* 56, 621–633. doi: 10.1016/j.rehab.2013.08.008

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., et al. (2013a). 7 degree-of-freedom neuroprosthetic control by an individual with tetraplegia. *Lancet* 381, 557–564. doi: 10.1016/S0140-6736(12)61816-9

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., et al. (2013b). High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* 381, 557–564. doi: 10.1016/S0140-6736(12)61816-9

Compston, A. (2010). Aids to the investigation of peripheral nerve injuries. Medical research council: nerve injuries research committee. His majesty's stationery office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the guarantors of brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. *Brain* 133, 2838–2844. doi: 10.1093/brain/awq270

Cornwall, R., and Hausman, M. R. (2004). Implanted neuroprostheses for restoration of hand function in tetraplegic patients. *J. Am. Acad. Orthop. Surg.* 12, 72–79.

Cortes, M., Elder, J., Rykman, A., Murray, L., Avedissian, M., Stampa, A., et al. (2013). Improved motor performance in chronic spinal cord injury following upper-limb robotic training. *NeuroRehabilitation* 33, 57–65. doi: 10.3233/NRE-130928

Cramer, S., Lastra, L., Lacourse, M., and Cohen, M. (2005). Brain motor system function after chronic, complete spinal cord injury. *Brain* 128, 2941–2950. doi: 10.1093/brain/awh648

Cramer, S., Orr, E., Cohen, M., and Lacourse, M. (2007). Effects of motor imagery training after chronic, complete spinal cord injury. *Exp. Brain Res.* 177, 233–242. doi: 10.1007/s00221-006-0662-9

Curt, A., Bruehlmeier, M., Leenders, K., Roelcke, U., and Dietz, V. (2002). Differential effect of spinal cord injury and functional impairment on human brain activation. *J. Neurotrauma* 19, 43–51. doi: 10.1089/089771502753460222 de Castro, M. C., and Cliquet, A. Jr. (2000a). Artificial sensorimotor integration in spinal cord injured subjects through neuromuscular and electrotactile stimulation. *Artif. Organs* 24, 710–717. doi: 10.1046/j.1525-1594.2000.06569.x

de Castro, M. C., and Cliquet, A. Jr. (2000b). An artificial grasping evaluation system for the paralysed hand. *Med. Biol. Eng. Comput.* 38, 275–280. doi: 10.1007/bf02347047

Decety, J., and Boisson, D. (1990). Effect of brain and spinal cord injuries on motor imagery. *Eur. Arch. Psychiatry Clin. Neurosci.* 240, 39–43. doi: 10.1007/bf02190091

Decety, J., and Grèzes, J. (1999). Neural mechanisms subserving the perception of human actions. *Trends Cogn. Sci.* 3, 172–178. doi: 10.1016/s1364-6613(99)01312-1

de los Reyes-Guzmán, A., Gil-Agudo, A., Peñasco-Martín, B., Solís-Mozos, M., del Ama-Espinosa, A., and Pérez-Rizo, E. (2010). Kinematic analysis of the daily activity of drinking from a glass in a population with cervical spinal cord injury. *J. Neuroeng. Rehabil.* 7:41. doi: 10.1186/1743-0003-7-41

De Mauro, A., Carrasco, E., Oyarzun, D., Ardanza, A., Frizera Neto, A., Torricelli, D., et al. (2011). Virtual reality system in conjunction with neurorobotics and neuroprosthetics for rehabilitation of motor disorders. *Stud. Health Technol. Inform.* 163, 163–165. doi: 10.3233/978-1-60750-706-2-163

de Morton, N. A. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust. J. Physiother.* 55, 129–133. doi: 10.1016/s0004-9514(09)70043-1

Di Rienzo, F., Collet, C., Hoyek, N., and Guillot, A. (2014a). Impact of neurological deficits on motor imagery: a systematic review of clinical evaluations. *Neuropsychol. Rev.* 24, 116–147. doi: 10.1007/s11065-014-9257-6

Di Rienzo, F., Guillot, A., Daligault, S., Delpuech, C., Rode, G., and Collet, C. (2014b). Motor inhibition during motor imagery: a MEG study with a quadriplegic patient. *Neurocase* 20, 524–539. doi: 10.1080/13554794.2013.826685

Di Rienzo, F., Guillot, A., Mateo, S., Daligault, S., Delpuech, C., Rode, G., et al. (2014c). Neuroplasticity of prehensile neural networks after quadriplegia. *Neuroscience* 22, 82–92. doi: 10.1016/j.neuroscience.2014.05.021

Di Rienzo, F., Guillot, A., Mateo, S., Daligault, S., Delpuech, C., Rode, G., et al. (2015). Neuroplasticity of imagined wrist actions after spinal cord injury: a pilot study. *Exp. Brain Res.* 233, 291–302. doi: 10.1007/s00221-014-4114-7

Doyon, J., and Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Curr. Opin. Neurobiol.* 15, 161–167. doi: 10.1016/j.conb.2005.03.004

Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., et al. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav. Brain Res.* 199, 61–75. doi: 10.1016/j.bbr.2008.11.012

Driskell, J. E., Copper, C., and Moran, A. (1994). Does mental practice enhance performance? *J. Appl. Psychol.* 79, 481–492. doi: 10.1037/0021-9010.79.4.481

Dunlop, S. (2008). Activity-dependent plasticity: implications for recovery after spinal cord injury. *Trends Neurosci.* 31, 410–418. doi: 10.1016/j.tins.2008.05.004

Enzinger, C., Ropele, S., Fazekas, F., Loitfelder, M., Gorani, F., Seifert, T., et al. (2008). Brain motor system function in a patient with complete spinal cord injury following extensive brain-computer interface training. *Exp. Brain Res.* 190, 215–223. doi: 10.1007/s00221-008-1465-y

Erfani, A., and Erfanian, A. (2004). The effects of mental practice and concentration skills on EEG brain dynamics during motor imagery using independent component analysis. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 1, 239–242. doi: 10.1109/iembs.2004.1403136

Erfanian, A., and Erfani, A. (2004). ICA-based classification scheme for EEG-based brain-computer interface: the role of mental practice and concentration skills. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 1, 235–238. doi: 10.1109/iembs.2004.1403135

Faller, J., Scherer, R., Friedrich, E. V. C., Costa, U., Opisso, E., Medina, J., et al. (2014). Non-motor tasks improve adaptive brain-computer interface performance in users with severe motor impairment. *Front. Neurosci.* 8:320. doi: 10.3389/fnins.2014.00320

Fiori, F., Sedda, A., Ferrè, E. R., Toraldo, A., Querzola, M., Pasotti, F., et al. (2014). Motor imagery in spinal cord injury patients: moving makes the difference. *J. Neuropsychol.* 8, 199–215. doi: 10.1111/jnp.12020

Flanagin, V. L., Wutte, M., Glasauer, S., and Jahn, K. (2009). Driving dreams: cortical activations during imagined passive and active whole body movement. *Ann. N Y Acad. Sci.* 1164, 372–375. doi: 10.1111/j.1749-6632.2009.03844.x

Graimann, B., Allison, B., and Pfurtscheller, G. (eds). (2010). *Brain-computer interfaces: revolutionizing human-computer interaction.* Heidelberg: Springer.

Grangeon, M., Revol, P., Guillot, A., Rode, G., and Collet, C. (2012a). Could motor imagery be effective in upper limb rehabilitation of individuals with spinal cord injury? A case study. *Spinal Cord* 50, 766–771. doi: 10.1038/sc.2012.41

Grangeon, M., Charvier, K., Guillot, A., Rode, G., and Collet, C. (2012b). Using sympathetic skin responses in individuals with spinal cord injury as a quantitative evaluation of motor imagery abilities. *Phys. Ther.* 92, 831–840. doi: 10.2522/ptj.20110351

Grangeon, M., Guillot, A., Sancho, P.-O., Picot, M., Revol, P., Rode, G., et al. (2010). Rehabilitation of the elbow extension with motor imagery in a patient with quadriplegia after tendon transfer. *Arch. Phys. Med. Rehabil.* 91, 1143–1146. doi: 10.1016/j.apmr.2010.04.011

Grosjean, M., Shiffrar, M., and Knoblich, G. (2007). Fitts's law holds for action perception. *Psychol. Sci.* 18, 95–99. doi: 10.1111/j.1467-9280.2007.01854.x

Grosprêtre, S., Ruffino, C., and Lebon, F. (2015). Motor imagery and cortico-spinal excitability: a review. *Eur. J. Sport Sci.* doi: 10.1080/17461391.2015.1024756 [Epub ahead of print].

Grush, R. (2004). The emulation theory of representation: motor control, imagery and perception. *Behav. Brain Sci.* 27, 377–396; discussion 396–442. doi: 10.1017/s0140525x04000093

Guillot, A., Di Rienzo, F., and Collet, C. (2014). "The neurofunctional architecture of motor imagery," in *Advanced Brain Neuroimaging Topics in Health and Disease-Methods and Applications*, eds T. D. Papageorgiou, G. I. Christopoulos, and S. M. Smirnakis (Rijeka: InTech), 433–456.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., et al. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336, 924–926. doi: 10.1136/bmj.39489.470347.ad

Hanakawa, T., Dimyan, M. A., and Hallett, M. (2008). Motor planning, imagery and execution in the distributed motor network: a time-course study with functional MRI. *Cereb. Cortex* 18, 2775–2788. doi: 10.1093/cercor/bhn036

Hoffmann, G., Laffont, I., and Roby-Brami, A. (2002). Co-ordination of reaching movements in patients with cervical spinal cord injury. *Curr. Psychol. Cognit.* 21, 305–340. doi: 10.1038/sj.sc.3101277

Jackson, P. L., Lafleur, M. F., Malouin, F., Richards, C., and Doyon, J. (2001). Potential role of mental practice using motor imagery in neurologic rehabilitation. *Arch. Phys. Med. Rehabil.* 82, 1133–1141. doi: 10.1053/apmr.2001.24286

Jeannerod, M. (1984). The timing of natural prehension movements. *J. Mot. Behav.* 16, 235–254. doi: 10.1080/00222895.1984.10735319

Jeannerod, M. (1994). The representing brain: neural correlates of motor intention and imagery. *Behav. Brain Sci.* 17, 187–202. doi: 10.1017/s0140525x00034026

Jurkiewicz, M. T., Mikulis, D. J., McIlroy, W. E., Fehlings, M. G., and Verrier, M. C. (2007). Sensorimotor cortical plasticity during recovery following spinal cord injury: a longitudinal fMRI study. *Neurorehabil. Neural Repair* 21, 527–538. doi: 10.1177/1545968307301872

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., et al. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proc. Natl. Acad. Sci. U S A* 95, 861–868. doi: 10.1073/pnas.95.3.861

Kirshblum, S. C., Priebe, M. M., Ho, C. H., Scelza, W. M., Chiodo, A. E., and Wuermser, L.-A. (2007). Spinal cord injury medicine. 3. Rehabilitation phase after acute spinal cord injury. *Arch. Phys. Med. Rehabil.* 88, S62–S70. doi: 10.1016/j.apmr.2006.12.003

Kokotilo, K. J., Eng, J. J., and Curt, A. (2009). Reorganization and preservation of motor control of the brain in spinal cord injury: a systematic review. *J. Neurotrauma* 26, 2113–2126. doi: 10.1089/neu.2008.0688

Kondo, T., Saeki, M., Hayashi, Y., Nakayashiki, K., and Takata, Y. (2014). Effect of instructive visual stimuli on neurofeedback training for motor imagery-based brain-computer interface. *Hum. Mov. Sci.* doi: 10.1016/j.humov.2014.08.014 [Epub ahead of print].

Lacourse, M. (1999). Cortical potentials during imagined movements in individuals with chronic spinal cord injuries. *Behav. Brain Res.* 104, 73–88. doi: 10.1016/s0166-4328(99)00052-2

Laffont, I., Biard, N., Chalubert, G., Delahoche, L., Marhic, B., Boyer, F. C., et al. (2009). Evaluation of a graphic interface to control a robotic grasping arm: a multicenter study. *Arch. Phys. Med. Rehabil.* 90, 1740–1748. doi: 10.1016/j.apmr.2009.05.009

Laffont, I., Briand, E., Dizien, O., Combeaud, M., Bussel, B., Revol, M., et al. (2000). Kinematics of prehension and pointing movements in C6 quadriplegic patients. *Spinal Cord* 38, 354–362. doi: 10.1038/sj.sc.3100999

Laffont, I., Hoffmann, G., Dizien, O., Revol, M., and Roby-Brami, A. (2007). How do C6/C7 tetraplegic patients grasp balls of different sizes and weights? Impact of surgical musculo-tendinous transfers. *Spinal Cord* 45, 502–512. doi: 10.1038/sj.sc.3102047

Long, C., and Lawton, E. (1955). Functional significance of spinal cord lesion level. *Arch. Phys. Med. Rehabil.* 36, 249–255.

López-Larraz, E., Antelis, J. M., Montesano, L., Gil-Agudo, A., and Minguez, J. (2012). Continuous decoding of motor attempt and motor imagery from EEG activity in spinal cord injury patients. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 1798–1801. doi: 10.1109/embc.2012.6346299

Lotze, M., and Halsband, U. (2006). Motor imagery. *J. Physiol. Paris* 99, 386–395. doi: 10.1016/j.jphysparis.2006.03.012

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., and Elkins, M. (2003). Reliability of the pedro scale for rating quality of randomized controlled trials. *Phys. Ther.* 83, 713–721.

Malik, W. Q., Hochberg, L. R., Donoghue, J. P., and Brown, E. N. (2015). Modulation depth estimation and variable selection in state-space models for neural interfaces. *IEEE Trans. Biomed. Eng.* 62, 570–581. doi: 10.1109/tbme.2014.2360393

Martin, R., Johnston, K., and Sadowsky, C. (2012). Neuromuscular electrical stimulation-assisted grasp training and restoration of function in the tetraplegic hand: a case series. *Am. J. Occup. Ther.* 66, 471–477. doi: 10.5014/ajot.2012.003004

Mateo, S., Roby-Brami, A., Reilly, K., Rossetti, Y., Collet, C., and Rode, G. (2015a). Upper limb kinematics after cervical spinal cord injury: a review. *J. Neuroeng. Rehabil.* 12:9. doi: 10.1186/1743-0003-12-9

Mateo, S., Di Rienzo, F., Reilly, K. T., Revol, P., Delpuech, C., Daligault, S., et al. (2015b). Improvement of grasping after motor imagery in C6–C7 tetraplegia: a kinematic and MEG pilot study. *Restor. Neurol. Neurosci.* 33, 543–555. doi: 10.3233/RNN-140466

Mateo, S., Revol, P., Fourtassi, M., Rossetti, Y., Collet, C., and Rode, G. (2013). Kinematic characteristics of tenodesis grasp in C6 quadriplegia. *Spinal Cord* 51, 144–149. doi: 10.1038/sc.2012.101

Memberg, W. D., and Crago, P. E. (2000). An analysis of the input-output properties of neuroprosthetic hand grasps. *J. Rehabil. Res. Dev.* 37, 11–21.

Miller, K. J., Schalk, G., Fetz, E. E., den Nijs, M., Ojemann, J. G., and Rao, R. P. N. (2010). Cortical activity during motor execution, motor imagery and imagery-based online feedback. *Proc. Natl. Acad. Sci. U S A* 107, 4430–4435. doi: 10.1073/pnas.0913697107

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6:e1000097. doi: 10.1371/journal.pmed.1000097

Müller-Putz, G. R., Daly, I., and Kaiser, V. (2014). Motor imagery-induced EEG patterns in individuals with spinal cord injury and their impact on brain-computer interface accuracy. *J. Neural Eng.* 11:035011. doi: 10.1088/1741-2560/11/3/035011

Müller-Putz, G. R., Scherer, R., Pfurtscheller, G., and Neuper, C. (2010). Temporal coding of brain patterns for direct limb control in humans. *Front. Neurosci.* 4:34. doi: 10.3389/fnins.2010.00034

Müller-Putz, G. R., Scherer, R., Pfurtscheller, G., and Rupp, R. (2005). EEG-based neuroprosthesis control: a step towards clinical practice. *Neurosci. Lett.* 382, 169–174. doi: 10.1016/j.neulet.2005.03.021

Munzert, J., Lorey, B., and Zentgraf, K. (2009). Cognitive motor processes: the role of motor imagery in the study of motor representations. *Brain Res. Rev.* 60, 306–326. doi: 10.1016/j.brainresrev.2008.12.024

Nunome, H., Doyo, W., Sakurai, S., Ikegmai, Y., and Yabe, K. (2002). A kinematic study of the upper-limb motion of wheelchair basketball shooting in tetraplegic adults. *J. Rehabil. Res. Dev.* 39, 63–71.

Olsson, C.-J., and Nyberg, L. (2010). Motor imagery: if you can't do it, you won't think it. *Scand. J. Med. Sci. Sports* 20, 711–715. doi: 10.1111/j.1600-0838.2010.01101.x

Onose, G., Grozea, C., Anghelescu, A., Daia, C., Sinescu, C. J., Ciurea, A. V., et al. (2012). On the feasibility of using motor imagery EEG-based brain-computer interface in chronic tetraplegics for assistive robotic arm control: a clinical test and long-term post-trial follow-up. *Spinal Cord* 50, 599–608. doi: 10.1038/sc.2012.14

Paci, M., Matulli, G., Baccini, M., Rinaldi, L. A., and Baldassi, S. (2010). Reported quality of randomized controlled trials in neglect rehabilitation. *Neurol. Sci.* 31, 159–163. doi: 10.1007/s10072-009-0198-4

Papageorgiou, T. D., Lisinski, J. M., McHenry, M. A., White, J. P., and LaConte, S. M. (2013). Brain-computer interfaces increase whole-brain signal to noise. *Proc. Natl. Acad. Sci. U S A* 110, 13630–13635. doi: 10.1073/pnas.1210738110

Pfurtscheller, G. (2001). Functional brain imaging based on ERD/ERS. *Vision Res.* 41, 1257–1260. doi: 10.1016/s0042-6989(00)00235-2

Pfurtscheller, G., Guger, C., Müller, G., Krausz, G., and Neuper, C. (2000). Brain oscillations control hand orthosis in a tetraplegic. *Neurosci. Lett.* 292, 211–214. doi: 10.1016/s0304-3940(00)01471-3

Pfurtscheller, G., Leeb, R., Friedman, D., and Slater, M. (2008). Centrally controlled heart rate changes during mental practice in immersive virtual environment: a case study with a tetraplegic. *Int. J. Psychophysiol.* 68, 1–5. doi: 10.1016/j.ijpsycho.2007.11.003

Pfurtscheller, G., Neuper, C., Müller, G. R., Obermaier, B., Krausz, G., Schlögl, A., et al. (2003a). Graz-BCI: state of the art and clinical applications. *IEEE Trans. Neural Syst. Rehabil. Eng.* 11, 177–180. doi: 10.1109/tnsre.2003.814454

Pfurtscheller, G., Müller, G. R., Pfurtscheller, J., Gerner, H. J., and Rupp, R. (2003b). "Thought"—control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. *Neurosci. Lett.* 351, 33–36. doi: 10.1016/s0304-3940(03)00947-9

Pfurtscheller, J., Rupp, R., Müller, G. R., Fabsits, E., Korisek, G., Gerner, H. J., et al. (2005). [Functional electrical stimulation instead of surgery? Improvement of grasping function with FES in a patient with C5 tetraplegia]. *Unfallchirurg* 108, 587–590. doi: 10.1007/s00113-004-0876-x

Ranganathan, V. K., Siemionow, V., Liu, J. Z., Sahgal, V., and Yue, G. H. (2004). From mental power to muscle power—gaining strength by using the mind. *Neuropsychologia* 42, 944–956. doi: 10.1016/j.neuropsychologia.2003.11.018

Remy-Neris, O., Milcamps, J., Chikhi-Keromest, R., Thevenon, A., Bouttens, D., and Bouilland, S. (2003). Improved kinematics of unrestrained arm raising in C5–C6 tetraplegic subjects after deltoid-to-triceps transfer. *Spinal Cord* 41, 435–445. doi: 10.1038/sj.sc.3101481

Robinson, M. A., Barton, G. J., Lees, A., and Sett, P. (2010). Analysis of tetraplegic reaching in their 3D workspace following posterior deltoid-triceps tendon transfer. *Spinal Cord* 48, 619–627. doi: 10.1038/sc.2009.193

Rohm, M., Schneiders, M., Müller, C., Kreilinger, A., Kaiser, V., Müller-Putz, G. R., et al. (2013). Hybrid brain-computer interfaces and hybrid neuroprostheses for restoration of upper limb functions in individuals with high-level spinal cord injury. *Artif. Intell. Med.* 59, 133–142. doi: 10.1016/j.artmed.2013.07.004

Roy, F. D., Zewdie, E. T., and Gorassini, M. A. (2011). Short-interval intracortical inhibition with incomplete spinal cord injury. *Clin. Neurophysiol.* 122, 1387–1395. doi: 10.1016/j.clinph.2010.11.020

Saxena, S., Nikolić, S., and Popović, D. (1995). An EMG-controlled grasping system for tetraplegics. *J. Rehabil. Res. Dev.* 32, 17–24.

Scherer, R., Faller, J., Friedrich, E. V. C., Opisso, E., Costa, U., Kübler, A., et al. (2015). Individually adapted imagery improves brain-computer interface performance in end-users with disability. *PLoS One* 10:e0123727. doi: 10.1371/journal.pone.0123727

Schill, O., Wiegand, R., Schmitz, B., Matthies, R., Eck, U., Pylatiuk, C., et al. (2011). OrthoJacket: an active FES-hybrid orthosis for the paralysed upper extremity. *Biomed. Tech. (Berl)* 56, 35–44. doi: 10.1515/bmt.2010.056

Shimada, Y., Chida, S., Matsunaga, T., Misawa, A., Ito, H., Sakuraba, T., et al. (2003). Grasping power by means of functional electrical stimulation in a case of C6 complete tetraplegia. *Tohoku J. Exp. Med.* 201, 91–96. doi: 10.1620/tjem.201.91

Siedziewski, L., Schaaf, R. C., and Mount, J. (2012). Use of robotics in spinal cord injury: a case report. *Am. J. Occup. Ther.* 66, 51–58. doi: 10.5014/ajot.2012.000943

Smits-Engelsman, B. C. M., and Wilson, P. H. (2013). Age-related changes in motor imagery from early childhood to adulthood: probing the internal representation of speed-accuracy trade-offs. *Hum. Mov. Sci.* 32, 1151–1162. doi: 10.1016/j.humov.2012.06.006

Stinear, C. (2010). "Corticospinal facilitation during motor imagery," in *The Neurophysiological Foundations of Mental and Motor Imagery*, eds A. Guillot and C. Collet (Oxford: Oxford University Press), 47–61.

Szpunar, K. K., Watson, J. M., and McDermott, K. B. (2007). Neural substrates of envisioning the future. *Proc. Natl. Acad. Sci. U S A* 104, 642–647. doi: 10.1073/pnas.0610082104

Tate, R. L., McDonald, S., Perdices, M., Togher, L., Schultz, R., and Savage, S. (2008). Rating the methodological quality of single-subject designs and n-of-1 trials: introducing the single-case experimental design (SCED) scale. *Neuropsychol. Rehabil.* 18, 385–401. doi: 10.1080/09602010802009201

Taylor, P., Esnouf, J., and Hobby, J. (2002). The functional impact of the freehand system on tetraplegic hand function. Clinical results. *Spinal Cord* 40, 560–566. doi: 10.1038/sj.sc.3101373

Tcheang, L., Bülthoff, H. H., and Burgess, N. (2011). Visual influence on path integration in darkness indicates a multimodal representation of large-scale space. *Proc. Natl. Acad. Sci. U S A* 108, 1152–1157. doi: 10.1073/pnas.1011843108

Thorsen, R., Binda, L., Chiaramonte, S., Dalla Costa, D., Redaelli, T., Occhi, E., et al. (2014). Correlation among lesion level, muscle strength and hand function in cervical spinal cord injury. *Eur. J. Phys. Rehabil. Med.* 50, 31–38.

Thorsen, R., Spadone, R., and Ferrarin, M. (2001). A pilot study of myoelectrically controlled FES of upper extremity. *IEEE Trans. Neural Syst. Rehabil. Eng.* 9, 161–168. doi: 10.1109/7333.928576

Tidoni, E., Tieri, G., and Aglioti, S. M. (2015). Re-establishing the disrupted sensorimotor loop in deafferented and deefferented people. The case of spinal cord injuries. *Neuropsychologia* doi: 10.1016/j.neuropsychologia.2015.06.029 [Epub ahead of print].

Vahdat, S., Lungu, O., Cohen-Adad, J., Marchand-Pauvert, V., Benali, H., and Doyon, J. (2015). Simultaneous brain-cervical cord fMRI reveals intrinsic spinal cord plasticity during motor sequence learning. *PLoS Biol.* 13:e1002186. doi: 10.1371/journal.pbio.1002186

Viswanathan, S., Fritz, C., and Grafton, S. T. (2012). Telling the right hand from the left hand: multisensory integration, not motor imagery, solves the problem. *Psychol. Sci.* 23, 598–607. doi: 10.1177/0956797611429802

Vučković, A., Wallace, L., and Allan, D. B. (2015). Hybrid brain-computer interface and functional electrical stimulation for sensorimotor training in participants with tetraplegia: a proof-of-concept study. *J. Neurol. Phys. Ther.* 39, 3–14. doi: 10.1097/npt.0000000000000063

Warner, L., and McNeill, M. E. (1988). Mental imagery and its potential for physical therapy. *Phys. Ther.* 68, 516–521.

Wilson, M. (2003). Imagined movements that leak out. *Trends Cogn. Sci.* 7, 53–55. doi: 10.1016/s1364-6613(02)00041-4

Wodlinger, B., Downey, J. E., Tyler-Kabara, E. C., Schwartz, A. B., Boninger, M. L., and Collinger, J. L. (2015). Ten-dimensional anthropomorphic arm control in a human brain-machine interface: difficulties, solutions and limitations. *J. Neural Eng.* 12:016011. doi: 10.1088/1741-2560/12/1/016011

Woolsey, R. (1985). Rehabilitation outcome following spinal cord injury. *Arch. Neurol.* 42, 116–119. doi: 10.1001/archneur.1985.04060020026008

Yuan, H., and He, B. (2014). Brain-computer interfaces using sensorimotor rhythms: current state and future perspectives. *IEEE Trans. Biomed. Eng.* 61, 1425–1435. doi: 10.1109/tbme.2014.2312397

Yue, G., and Cole, K. J. (1992). Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J. Neurophysiol.* 67, 1114–1123.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 15 September 2015
doi: 10.3389/fnbeh.2015.00253

Brain-derived neurotrophic factor serum levels correlate with cognitive performance in Parkinson's disease patients with mild cognitive impairment

Alberto Costa[1,2]*, *Antonella Peppe*[2], *Giovanni Augusto Carlesimo*[2,3], *Silvia Zabberoni*[2], *Francesco Scalici*[2], *Carlo Caltagirone*[2,3] *and Francesco Angelucci*[2]

[1] *Niccolò Cusano University, Rome, Italy,* [2] *IRCCS, Fondazione Santa Lucia, Rome, Italy,* [3] *Tor Vergata University, Rome, Italy*

OPEN ACCESS

Edited by:
Benedetto Sacchetti, University of Turin, Italy

Reviewed by:
Félix Javier Jiménez-Jiménez, Hospital del Sureste, Spain
Marco Cambiaghi, University of Turin, Italy

***Correspondence:**
Alberto Costa, Niccolò Cusano University, Via Don Carlo Gnocchi 3, 00166-Roma; IRCCS Fondazione Santa Lucia, Via Ardeatina 306, 00179-Roma, Italy
alberto.costa@unicusano.it; a.costa@hsantalucia.it

Received: *11 May 2015*
Accepted: *31 August 2015*
Published: *15 September 2015*

Citation:
Costa A, Peppe A, Carlesimo GA, Zabberoni S, Scalici F, Caltagirone C and Angelucci F (2015) Brain-derived neurotrophic factor serum levels correlate with cognitive performance in Parkinson's disease patients with mild cognitive impairment. Front. Behav. Neurosci. 9:253. doi: 10.3389/fnbeh.2015.00253

Brain-derived neurotrophic factor (BDNF) is a trophic factor regulating cell survival and synaptic plasticity. Recent findings indicate that BDNF could be a potential regulatory factor for cognitive functioning in normal and/or neuropathological conditions. With regard to neurological disorders, recent data suggest that individuals with Parkinson's disease (PD) may be affected by cognitive deficits and that they have altered BDNF production. Therefore, the hypothesis can be advanced that BDNF levels are associated with the cognitive state of these patients. With this in mind, the present study was aimed at exploring the relationship between BDNF serum levels and cognitive functioning in PD patients with mild cognitive impairment (MCI). Thirteen PD patients with MCI were included in the study. They were administered an extensive neuropsychological test battery that investigated executive, episodic memory, attention, visual-spatial and language domains. A single score was obtained for each cognitive domain by averaging *z*-scores on tests belonging to that specific domain. BDNF serum levels were measured by enzyme-linked immunoassay (ELISA). Pearson's correlation analyses were performed between BDNF serum levels and cognitive performance. Results showed a significant positive correlation between BDNF serum levels and both attention ($p < 0.05$) and executive ($p < 0.05$) domains. Moreover, in the executive domain we found a significant correlation between BDNF levels and scores on tests assessing working memory and self-monitoring/inhibition. These preliminary data suggest that BDNF serum levels are associated with cognitive state in PD patients with MCI. Given the role of BDNF in regulating synaptic plasticity, the present findings give further support to the hypothesis that this trophic factor may be a potential biomarker for evaluating cognitive changes in PD and other neurological syndromes associated with cognitive decline.

Keywords: BDNF, Parkinson's disease, cognitive functions, mild cognitive impairment, neuropsychological deficits

Introduction

Brain-derived neurotrophic factor (BDNF) belongs to the family of neurotrophins that regulate the survival and functioning of neurons in the central nervous system (Baydyuk and Xu, 2014). BDNF was originally described as a trophic factor for dopaminergic neurons of the substantia nigra (Hyman et al., 1991). However, successive studies found that its action on neurons is not only trophic but involves the regulation of synaptic plasticity through the activation of signal transduction pathways that influence the release of neurotransmitters such as glutamate and GABA (Gottmann et al., 2009). These effects on synaptic transmission have been associated with the long-term potentiation that takes place in the hippocampus during learning and memory processes (Leal et al., 2014). Thus, BDNF not only has a trophic action but also the potential to regulate cognitive processes.

In recent years, the latter role of BDNF was confirmed in both animal and human studies. In rodent models, it was shown that knockout of the BDNF gene affects spatial learning and memory (Gorski et al., 2003; Monteggia et al., 2004; Heldt et al., 2007), whereas transgenic overexpression of BDNF in cortical and subcortical (i.e., hippocampus) regions sustains performance (Koponen et al., 2004). Li et al. (2012) also documented that, in cognitively affected rats, BDNF infusion into the nucleus accumbens improved cognition, synaptic plasticity and cell signaling. As for human data, in both healthy individuals (Alfimova et al., 2012) and in persons with psychiatric disturbances (Lu et al., 2012; Tükel et al., 2012), BDNF gene polymorphism (Val66Met) was found to be associated with executive dysfunctions. In a sample of more than 50 healthy young subjects, Koven and Collins (2014) recently documented a significant correlation between (urinary) BDNF concentration and cognitive performance on tests tapping cognitive flexibility (i.e., Trail Making Test, Design Fluency and Verbal Category Switching). Nonetheless the role of BDNF gene polymorphism in Parkinson's disease (PD) is not well defined and the results are sometimes contradictory. While some authors report an association between gene polymorphism with cognitive impairments in PD patients (Foltynie et al., 2005; Guerini et al., 2009) or with the onset of the disease (Karamohamed et al., 2005), other studies do not show such correlations (Dai et al., 2013; Svetel et al., 2013; Białecka et al., 2014). Many of these studies however are not strictly comparable in term of disease stages and the methodology used to assess cognitive impairments (Alonso-Navarro et al., 2014; Białecka et al., 2014). Thus, the results do not permit definitive conclusions. Larger sample-size and multiethnicity studies with homogeneous PD patients and well-matched controls are needed in the future study.

Above data indicate that BDNF could be a potential regulatory factor for cognitive functioning in normal and/or neuropathological conditions. Among the neurological disorders affected by cognitive deficits, PD is interesting because the neuronal pathways affected are involved in some cognitive functions that respond to the action of BDNF (Murer et al., 2001; Guillin et al., 2003). In fact, PD is characterized by dopamine cell loss within the substantia nigra that causes a precocious deafferentation of the nigro-striatal dopamine pathway with later involvement of the meso-cortical and mesolimbic dopamine pathways (Yeterian and Pandya, 1991; Jahanshahi et al., 2010). Thus, in addition to motor disorders PD patients may also present cognitive deficits including mild cognitive impairment (MCI) and dementia (Robbins and Cools, 2014). Typically PD patients with cognitive deficits have a dysexecutive profile that is characterized by poor performance on tests tapping shifting and planning (Cools, 2006; Cools and D'Esposito, 2011; MacDonald and Monchi, 2011), working memory (Cools, 2006; Cools and D'Esposito, 2011) and free recall of studied information (Costa et al., 2014a). As stated before, BDNF is a trophic factor for the dopaminergic neurons of these brain regions. Indeed, many studies have shown that PD patients show decreased BDNF levels in the substantia nigra (pars compacta; Howells et al., 2000) and in serum (Scalzo et al., 2010). Moreover, BDNF serum concentration was associated to the level of dopamine transporter binding in the striatum (Ziebell et al., 2012).

Studies on cerebrospinal fluid (CSF) of PD patients revealed an association between BDNF and cognitive performance (Leverenz et al., 2011) and increased BDNF levels compared with controls (Salehi and Mashayekhi, 2009). Moreover, CSF BDNF levels were found to be reduced in PD patients with major depression (MD) as compared to solely depressed patients after treatment with antidepressants (citalopram; Pålhagen et al., 2010). Despite these studies, the role of CSF BDNF levels as biomarker in PD needs to be replicated according to more strictly diagnostic standardized criteria and in longer follow- up periods (Jiménez-Jiménez et al., 2014).

Altogether these findings suggest that BDNF serum levels may not only be a trait that characterizes dopaminergic dysfunctions in PD patients but could also be a potential biomarker of their cognitive deficits. To test this hypothesis, we performed a pilot study with a groups of individuals with PD and MCI, in which we assessed BDNF serum levels and correlated them with scores obtained on tests measuring episodic memory, language, attention, executive and visual-spatial functions. Since in humans BDNF has been reported to correlate with specific components of the executive domain that are precociously weakened in PD (Koven and Collins, 2014), we expected to find a significant association between BDNF serum levels and PD patients' performance on executive tests.

Materials and Methods

Patients

We recruited 13 right-handed subjects with idiopathic PD who gave their written informed consent. The study was approved by Ethics Committee of the Santa Lucia Foundation. The United Kingdom PD Society brain bank criteria were used to diagnosis PD (Hughes et al., 1992).

MCI was diagnosed according to the criteria of Litvan et al. (2012). Accordingly, to be included PD subjects patients have a performance that was 1.5 SD below the average performance from the average performance of the normal population on at least one neuropsychological test investigating executive abilities and on another test sensitive to short-term memory/attention, visual-spatial abilities, episodic memory and language (the neuropsychological test battery is described below). The Mini-Mental State Examination (MMSE; Folstein et al., 1975) score had to be ≥26. In order to exclude psychiatric diseases, neurological conditions other than PD, vascular brain damage and major systemic or metabolic pathologies that could influence cognitive performance, we performed neuropsychiatric, neuroradiological (CT or MR) and laboratory examinations.

In order to assess functional abilities in daily living and their relationship with cognitive functioning we administered the Clinical Dementia Rating Scale, the Instrumental Activities of Daily Living scale (Lawton and Brody, 1969) and the Pill questionnaire (Dubois et al., 2007). Severity of depressive and apathy symptoms was also assessed by administering the Beck Depression Inventory (Beck et al., 1961; Visser et al., 2009) and the Apathy Evaluation Scale—self version (Marin et al., 1991; Leentjens et al., 2008), respectively. PD patients were being treated with levodopa and/or dopamine agonists (ropinirole, pramipexole and rotigotine) during examination period. The levodopa equivalent and the clinical and sociodemographic characteristics of the group are reported in **Table 1**. Twenty healthy controls (HC) were also recruited. Inclusion criteria for HC were: (i) absence of subjective cognitive deficits and (ii) MMSE score ≥26 (Folstein et al., 1975). Exclusion criteria were: (i) performance 1.5 SD below the normative population on any test of the standardized neuropsychological screening battery; (ii) current or previous neurological or psychiatric disorders, major systemic or metabolic diseases that could potentially affect cognitive functioning; and (iii) taking medications that have an effect on brain functioning. HC were only administered the behavioral tests.

TABLE 1 | Socio-demographic and clinical characteristics of the samples.

	Mean (SD)			
	PD patients	Healthy controls	*F* values	*p* values
Age	68.3 (7.8)	66.4 (7.4)	0.48	>0.40
Years of formal education	11.2 (4.9)	12.4 (3.3)	0.71	>0.40
Mini mental state examination	28.1 (1.5)	29.4 (0.7)	12.1	0.001
Pill questionnaire	3.3 (0.75)			
ADL	5.2 (1.3)			
IADL	7.1 (1.5)			
Beck depression inventory	7.8 (5.6)	6.7 (5.8)	0.25	>0.60
Apathy evaluation scale	32.3 (6.8)	28.0 (6.1)	3.05	0.093
Disease duration	8.8 (6.9)			
Daily levodopa equivalents	695 (294)			
UPDRS part-III	26.5 (11.1)			

UPDRS, Unified Parkinson's Disease Rating Scale.

Socio-demographic and clinical characteristics of individuals participating to the study are reported in **Table 1**.

Neuropsychological Test Battery

The following neuropsychological tests were administered to subjects according to the domain they assess: (a) Episodic memory: Immediate and Delayed Recall of a 15-Word List (Carlesimo et al., 1996); Prose Recall (Carlesimo et al., 2002); Immediate and delayed reproduction of Rey's Figure (Carlesimo et al., 2002); (b) Attention and short-term memory: Digit Span and Corsi Block Tapping test Forward and Backward (Monaco et al., 2013); Trail Making Test -Part A (Giovagnoli et al., 1996); (c) Executive functions: Phonological Word Fluency (Carlesimo et al., 1996); Modified Card Sorting test (MCST; Nocentini et al., 2002); Raven's Coloured Progressive Matrices (Carlesimo et al., 1996); Trail Making Test—Part B (Giovagnoli et al., 1996); (d) Language: Objects and Verbs Naming subtests from the Neuropsychological Examination of Aphasia (Capasso and Miceli, 2001); and (e) Visual-spatial functions: Copy of Drawings and Copy of Drawings with Landmarks (Carlesimo et al., 1996); Copy of Rey's Figure (Carlesimo et al., 2002).

Additional tests were administered to assess executive functioning according to the ability they investigated: Zoo Map test (Wilson et al., 1998; planning and self-monitoring), Stroop test (Barbarotto et al., 1998; response inhibition and self-monitoring), Alternate Phonemic and Category fluency (Cognitive Flexibility/shifting) and Category Fluency (Costa et al., 2014c).

In order to standardize the measurement scales between the different tests, raw scores were transformed into z-scores by considering the means and standard deviations of the HC group.

First, a unique z-score was computed for each cognitive domain (i.e., episodic memory, attention and short-term memory, executive functions, language and visual-spatial domains) by averaging subjects' z-scores on tests belonging to that specific domain.

Following Koven and Collins (2014), to investigate the possible correlation between BDNF levels and specific components of the executive domain (abstract reasoning/planning, self-monitoring/response inhibition, cognitive flexibility, fluency and working memory), individual z-scores were computed for each executive component by averaging the subjects' z-scores on the relative tests. Thus, an individual score was obtained for abstract reasoning/planning (total accuracy score on the Zoo Map Test; number of categories achieved on the MCST; accuracy score on the Progressive Matrices), Self-monitoring/Response inhibition (Errors made on the Zoo Map Test; errors made and response times on interference condition of the Stroop test), Cognitive Flexibility (perseverative errors committed on the MCST; accuracy score on Alternate Phonemic and Semantic fluency; Trail Making Test Part B-Part A score), Fluency (Phonemic and Semantic fluency), and Working memory (Digit and Corsi span backward). All z-scores were considered as absolute values so that higher scores corresponded to better performance.

Blood Sampling

Blood samples were collected between 8:00 a.m. and 10:00 a.m., centrifuged at 2000×g for 20 min and stored at −80°C until analysis (Angelucci et al., 2015).

Determination of BDNF Content

BDNF was detected in sandwich enzyme-linked immunoassay (ELISA; R&D Systems, USA; cat. N° DY248) according to the manufacturer's instructions as previously described (Angelucci et al., 2015). Wells were developed with tetramethylbenzidine and measured at 450/570 nm and BDNF content was quantified against a standard curve calibrated with known amounts of protein. The detection limit for BDNF was 15 pg/ml. Measurements were performed in duplicate and values are expressed as ng/ml. Cross-reactivity with other related trophic factors (NGF, NT-3; NT-4; TGFβ, TGFα) was less than 3% (Angelucci et al., 2015).

Statistical Analysis

In order to compare PD patients' and HCs' scores on the five main cognitive domains (episodic memory, attention and short-term memory, executive functions, language, visual-spatial functions), a multivariate analysis of variance (MANOVA) and individual univariate ANOVAS were carried out.

Pearson's r correlations were performed to examine the relationship between BDNF serum levels and *z*-scores obtained by PD patients in the different cognitive domains examined.

The same statistical analysis was used to examine the correlation between BDNF serum levels and PD patients' *z*-scores on the different executive components.

Results

Comparisons Between PD Patients and Healthy Controls

The *z*-scores obtained by the experimental subjects are illustrated in **Figure 1**. The MANOVA showed a significant effect ($F_{(5,27)} = 9.64$; $p < 0.001$). Subsequent univariate analyses showed that PD patients obtained significantly lower *z*-scores than HC in the cognitive domains of memory, executive functions, attention and visual-spatial abilities ($F_{(1,33)}$ range: 17.1–32.5; $p < 0.001$ in all cases). By contrast, in the language domain the between group difference only approached statistical significance ($F_{(1,33)} = 3.44$; $p = 0.073$).

Correlation Between BDNF Serum Levels and PD Patients' Cognitive Scores

Analysis Involving the Five Main Cognitive Domains

Results of Pearson's *r* correlation analyses showed a significant positive correlation between BDNF serum levels and PD patients' *z*-scores in the executive ($r = 0.62$; $p = 0.023$) and attention ($r = 0.59$; $p = 0.032$) domains. This indicates that better scores on the above tests were associated with a higher concentration of BDNF. The effects related to analyses involving the remaining three cognitive domains did not reach statistical significance (episodic memory: $r = -0.27$; $p = 0.36$; visual-spatial domain: $r = 0.33$; $p = 0.26$; language domain: $r = -0.05$; $p = 0.88$).

Analyses Involving the Different Components of the Executive Domain

A significant positive correlation was found between BDNF levels and *z*-scores referring to self-monitoring/response inhibition ($r = 0.68$; $p = 0.011$) and working memory ($r = 0.62$; $p = 0.025$) performance, indicating that higher BDNF levels were associated with better cognitive performance. The remaining analyses showed no significant effects (Planning/Abstraction: $r = 0.48$; $p = 0.098$; shifting: $r = 0.41$; $p = 0.17$; Fluency: $r = 0.06$; $p = 0.85$).

Discussion

This study investigated the association between cognitive functioning and BDNF serum level in PD patients with MCI. For this purpose, we administered an extensive neuropsychological battery to a sample of PD patients including tests for the assessment of episodic memory, executive functions, attention, language and visual-spatial abilities. The results showed a positive association between BDNF serum levels and performance on neuropsychological tests investigating executive functioning and attention. Moreover, other analyses focusing on the different components of the executive domain showed a

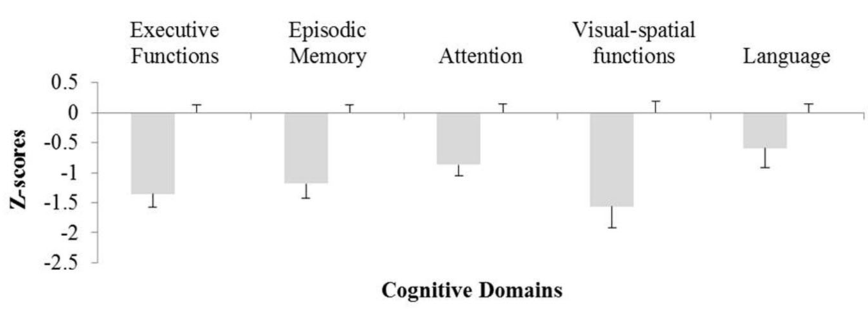


FIGURE 1 | Parkinson's disease (PD) patients' *z*-scores on the different cognitive domains examined. The *x* axis represents healthy controls (HC) values (averaged). Vertical bars represent standard errors.

closer association between BDNF levels and working memory and self-monitoring/inhibition.

Our results are congruent with previous data reported in both animal and human studies that documented an association between BDNF-related activity and cognitive functioning (Koven and Collins, 2014; Robbins and Cools, 2014), particularly with data suggesting a specific association with abilities in the executive system domain (Gajewski et al., 2011; Alfimova et al., 2012; Lu et al., 2012; Tükel et al., 2012; Koven and Collins, 2014). In fact, molecular studies reported that the BDNF gene polymorphism (Val66Met) may affect executive functions in healthy subjects (Alfimova et al., 2012) and in patients with psychiatric disturbances (Lu et al., 2012; Tükel et al., 2012). Very interestingly, Koven and Collins (2014), who adopted a design similar to ours, recently documented a significant relationship in healthy subjects between (urinary) BDNF concentration and performance on executive tests. These authors examined a sample of more than 50 healthy young subjects who were administered a neuropsychological test battery investigating different subcomponents of the executive system. Adopting a correlational design, they demonstrated that subjects' performance on tests tapping cognitive flexibility (i.e., Trail Making Test, Design Fluency and Verbal Category Switching) was positively associated with BDNF urinary concentrations. Our results differed from those of Koven and Collins in that we did not find a specific association between BDNF and set-shifting (although the relative correlation was in the expected direction). In fact, BDNF serum concentration correlated with the executive scores of working memory, self-monitoring and abstraction/planning. The imperfect congruence between our results and those of Koven and Collins' study is likely due to differences in the recruited samples. Indeed, the participants in Koven and Collins' study were healthy young individuals. Instead, our sample consisted of PD patients with a known cognitive weakness (i.e., MCI with a predominantly dysexecutive and amnestic neuropsychological profile).

BDNF plays a role in the promotion of the survival and function of striatal dopaminergic neurons and in regulating synaptic connectivity (Gómez-Palacio-Schjetnan and Escobar, 2013; He et al., 2013). Other studies have shown that BDNF brain and peripheral levels are decreased in PD patients as compared to HC (Scalzo et al., 2010). Moreover, Gyárfás et al. (2010) demonstrated that treatment with antiparkinsonian drugs may rise BDNF levels. As previously mentioned, PD is characterized by altered functioning of the brain dopamine systems, which involve the nigro-striatal, meso-cortical and mesolimbic pathways (Robbins and Cools, 2014). More specifically, dopamine deafferentation primarily involves the nigro-dorsal striatum pathways and dopamine projections to the dorsal prefrontal cortex (Baydyuk and Xu, 2014). In this regard, it has been hypothesised that in the early stages of PD dopamine altered activity is associated with cognitive weakness due to the regional distribution of dopamine receptor dysfunctioning (Cools and D'Esposito, 2011). In fact, dopamine depletion has an early effect on the striatal regions that are rich with D2 receptors, whose phasic activity is important for sustaining cognitive flexibility processes (Camps et al., 1990; Yeterian and Pandya, 1991; Agid et al., 1993; MacDonald and Monchi, 2011). Only later it involves the dorsal prefrontal cortex where tonic D1 activity sustains the ability to retain stable representations in the face of incoming information (i.e., resistance to interference, self-monitoring; Cohen et al., 2002; Frank, 2005; Costa et al., 2009, 2014b; Cools and D'Esposito, 2011). In fact, weakness of the executive system is a frequent and precocious finding in PD (Dirnberger and Jahanshahi, 2013). Therefore, our finding of a significant correlation between BDNF serum levels and prefrontal-related cognitive performance, although preliminarily, supports the hypothesis that BDNF activity contributes to maintaining normal prefrontal cortex functioning (Savitz et al., 2006; Woo and Lu, 2006; Galloway et al., 2008). In addition, the data presented here, together with the observation that BDNF is reduced in the brain and in the serum of PD patients, could suggest that the measurement of BDNF in serum may be used as a biological correlate of cognitive as well as motor functioning. The fact that BDNF levels positively correlate with performance on neuropsychological tests is encouraging. Although we demonstrated in a previous work that a cognitive rehabilitation protocol was able to increase BDNF serum levels and cognitive functions in PD patients affected by MCI, we did not find a significant correlation between the biological and neuropsychological data (Angelucci et al., 2015). As the number of patients was even smaller (7/8 patients per group) and only one measure of executive functioning was used, we can speculate that the lack of correlation in that study could have been due to both insufficient sample size and low sensitivity of the cognitive measure used to measure executive dysfunction in these patients.

Nonetheless, some limitations should be taken into account in the interpretation of our data. The study is limited by the poor sample size. Furthermore, we are merely describing an association between BDNF serum and cognitive performance and not a causal relationship. PD is now considered a multi-systemic neurodegenerative disorder that is characterized by a combination of motor and non-motor symptoms (Stacy, 2011). For a long time the main clinical focus in PD has been on the motor symptoms resulting from degeneration of the substantia nigra and the dopaminergic nigrostriatal pathway, but there is increasing recognition that other brain areas are involved in the manifestation of non motor symptoms (Rana et al., 2015) including the cerebral cortex (Lindenbach and Bishop, 2013), brainstem (Greene, 2014) and peripheral nervous system (Conte et al., 2013). Thus, alterations of BDNF brain and peripheral levels may occur in response to other deficits in these PD associated brain areas. This may limit the possibility to use BDNF as a possible marker of PD cognitive disturbances. Future studies, such as those using PET (Positron Emission Tomography), are needed to establish a direct correlation between dopaminergic denervation and BDNF.

In conclusion, this study shows that BDNF serum levels correlate positively with performance on neuropsychological tests investigating executive functioning and attention. These findings support the idea that this protein may represent a possible peripheral marker of cognitive functioning, although this hypothesis needs to be confirmed in larger cohorts of samples and with different methodologies.

Author Contributions

AC, AP made substantial contributions to the conception and design of the work, and the acquisition, analysis, and interpretation of data for the work; GAC made substantial contributions to the conception and design of the work; SZ and FS made substantial contributions to the the acquisition of data for the work; CC made substantial contributions to the conception and design of the work; FA made substantial contributions to the conception of the work, and to the acquisition, analysis, and interpretation of data for the work; all drafted the work and revised it critically for important intellectual content; gave final approval of the version to be published; and agreed 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 were appropriately investigated and resolved.

References

Agid, Y., Ruberg, M., Javoy-Agid, F., Hirsch, E., Raisman-Vozari, R., Vyas, S., et al. (1993). Are dopaminergic neurons selectively vulnerable to Parkinson's disease? *Adv. Neurol.* 60, 148–164.

Alfimova, M. V., Korovaitseva, G. I., Lezheiko, T. V., and Golimbet, V. E. (2012). Effect of BDNF Val66Met polymorphism on normal variability of executive functions. *Bull. Exp. Biol. Med.* 152, 606–609. doi: 10.1007/s10517-012-1587-x

Alonso-Navarro, H., Jimenez-Jimenez, F. J., Garcia-Martin, E., and Agundez, J. A. (2014). Genomic and pharmacogenomic biomarkers of Parkinson's disease. *Curr. Drug Metab.* 15, 129–181. doi: 10.2174/138920021502140327175404

Angelucci, F., Peppe, A., Carlesimo, G. A., Serafini, F., Zabberoni, S., Barban, F., et al. (2015). A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. *Front. Hum. Neurosci.* 9:130. doi: 10.3389/fnhum.2015.00130

Barbarotto, R., Laiacona, M., Frosio, R., Vecchio, M., Farinato, A., and Capitani, E. (1998). A normative study on visual reaction times and two stroop colour-word tests. *Ital. J. Neurol. Sci.* 19, 161–670. doi: 10.1007/bf00831566

Baydyuk, M., and Xu, B. (2014). BDNF signaling and survival of striatal neurons. *Front. Cell. Neurosci.* 8:254. doi: 10.3389/fncel.2014.00254

Beck, A. T., Ward, C. H., Mendelson, M., Mock, M., and Erbaugh, J. (1961). An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Białecka, M., Kurzawski, M., Roszmann, A., Robowski, P., Sitek, E. J., Honczarenko, K., et al. (2014). BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. *Neurosci. Lett.* 561, 86–90. doi: 10.1016/j.neulet.2013.12.051

Camps, M., Kelly, P. H., and Palacios, J. M. (1990). Autoradiographic localization of dopamine D1 and D2 receptors in the brain of several mammalian species. *J. Neural Transm. Gen. Sect.* 80, 105–127. doi: 10.1007/bf01257077

Capasso, R., and Miceli, G. (2001). *Esame Neuropsicologico Dell'Afasia.* Milano: Springer Verlag.

Carlesimo, G. A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., et al. (2002). Standardizzazione di due test di memoria per uso clinico: breve racconto e figura di Rey. *Nuova Riv. di Neurol.* 12, 1–13.

Carlesimo, G. A., Caltagirone, C., and Gainotti, G. (1996). The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. the group for the standardization of the mental deterioration battery. *Eur. Neurol.* 36, 378–384. doi: 10.1159/000117297

Cohen, J. D., Braver, T. S., and Brown, J. W. (2002). Computational perspectives on dopamine function in prefrontal cortex. *Curr. Opin. Neurobiol.* 12, 223–229. doi: 10.1016/s0959-4388(02)00314-8

Conte, A., Khan, N., Defazio, G., Rothwell, J. C., and Berardelli, A. (2013). Pathophysiology of somatosensory abnormalities in parkinson disease. *Nat. Rev. Neurol.* 9, 687–697. doi: 10.1038/nrneurol.2013.224

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neurosci. Biobehav. Rev.* 30, 1–23. doi: 10.1016/j.neubiorev.2005.03.024

Cools, R., and D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol. Psychiatry* 69, e113–e125. doi: 10.1016/j.biopsych.2011.03.028

Costa, A., Monaco, M., Zabberoni, S., Peppe, A., Perri, R., Fadda, L., et al. (2014a). Free and cued recall memory in Parkinson's disease associated with amnestic mild cognitive impairment. *PLoS One* 9:e86233. doi: 10.1371/journal.pone.0086233

Costa, A., Peppe, A., Mazzù, I., Longarzo, M., Caltagirone, C., and Carlesimo, G. A. (2014b). Dopamine treatment and cognitive functioning in individuals with Parkinson's disease: the "cognitive flexibility" hypothesis seems to work. *Behav. Neurol.* 2014:260896. doi: 10.1155/2014/260896

Costa, A., Bagoj, E., Monaco, M., Zabberoni, S., De Rosa, S., Papantonio, A. M., et al. (2014c). Standardization and normative data obtained in the Italian population for a new verbal fluency instrument, the phonemic/semantic alternate fluency test. *Neurol. Sci.* 35, 365–372. doi: 10.1007/s10072-013-1520-8

Costa, A., Peppe, A., Dell'Agnello, G., Caltagirone, C., and Carlesimo, G. A. (2009). Dopamine and cognitive functioning in de novo subjects with Parkinson's disease: effects of pramipexole and pergolide on working memory. *Neuropsychologia* 47, 1374–1381. doi: 10.1016/j.neuropsychologia.2009.01.039

Dai, L., Wang, D., Meng, H., Zhang, K., Fu, L., Wu, Y., et al. (2013). Association between the BDNF G196A and C270T polymorphisms and Parkinson's disease: a meta-analysis. *Int. J. Neurosci.* 123, 675–683. doi: 10.3109/00207454.2013.798784

Dirnberger, G., and Jahanshahi, M. J. (2013). Executive dysfunction in Parkinson's disease: a review. *J. Neuropsychol.* 7, 193–224. doi: 10.1111/jnp.12028

Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R. G., Broe, G. A., et al. (2007). Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov. Disord.* 22, 2314–2324. doi: 10.1002/mds.21844

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Foltynie, T., Lewis, S. G., Goldberg, T. E., Blackwell, A. D., Kolachana, B. S., Weinberger, D. R., et al. (2005). The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. *J. Neurol.* 252, 833–838. doi: 10.1007/s00415-005-0756-5

Frank, M. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and non-medicated parkinsonism. *J. Cogn. Neurosci.* 17, 51–72. doi: 10.1162/0898929052880093

Gajewski, P. D., Hengstler, J. G., Golka, K., Falkenstein, M., and Beste, C. (2011). The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly. *Neurobiol. Aging* 32, 2327.e7–2327.e19. doi: 10.1016/j.neurobiolaging.2011.06.010

Galloway, E. M., Woo, N. H., and Lu, B. (2008). Persistent neural activity in the prefrontal cortex: a mechanism by which bdnf regulates working memory? *Prog. Brain Res.* 169, 251–266. doi: 10.1016/s0079-6123(07)00015-5

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., and Capitani, E. (1996). Trail making test: normative values from 287 normal adults controls. *Ital. J. Neurol. Sci.* 17, 305–309. doi: 10.1007/bf01997792

Gómez-Palacio-Schjetnan, A., and Escobar, M. L. (2013). Neurotrophins and synaptic plasticity. *Curr. Top. Behav. Neurosci.* 15, 117–136. doi: 10.1007/7854_2012_231

Gorski, J. A., Balogh, S. A., Wehner, J. M., and Jones, K. R. (2003). Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. *Neuroscience* 121, 341–354. doi: 10.1016/s0306-4522(03)00426-3

Gottmann, K., Mittmann, T., and Lessmann, V. (2009). BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. *Exp. Brain Res.* 199, 203–234. doi: 10.1007/s00221-009-1994-z

Greene, J. G. (2014). Causes and consequences of degeneration of the dorsal motor nucleus of the vagus nerve in Parkinson's disease. *Antioxid. Redox. Signal.* 21, 649–667. doi: 10.1089/ars.2014.5859

Guerini, F. R., Beghi, E., Riboldazzi, G., Zangaglia, R., Pianezzola, C., Bono, G., et al. (2009). BDNF Val66Met polymorphism is associated with cognitive impairment in italian patients with Parkinson's disease. *Eur. J. Neurol.* 16, 1240–1245. doi: 10.1111/j.1468-1331.2009.02706.x

Guillin, O., Griffon, N., Bezard, E., Leriche, L., Diaz, J., Gross, C., et al. (2003). Brain-derived neurotrophic factor controls dopamine D3 receptor expression: therapeutic implications in Parkinson's disease. *Eur. J. Pharmacol.* 480, 89–95. doi: 10.1016/j.ejphar.2003.08.096

Gyárfás, T., Knuuttila, J., Lindholm, P., Rantamäki, T., and Castrén, E. (2010). Regulation of brain-derived neurotrophic factor (BDNF) and cerebral dopamine neurotrophic factor (CDNF) by anti-parkinsonian drug therapy *in vivo*. *Cell. Mol. Neurobiol.* 30, 361–368. doi: 10.1007/s10571-009-9458-3

He, Y. Y., Zhang, X. Y., Yung, W. H., Zhu, J. N., and Wang, J. J. (2013). Role of BDNF in central motor structures and motor diseases. *Mol. Neurobiol.* 48, 783–793. doi: 10.1007/s12035-013-8466-y

Heldt, S. A., Stanek, L., Chhatwal, J. P., and Ressler, K. J. (2007). Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol. Psychiatry* 12, 656–670. doi: 10.1038/sj.mp.4001957

Howells, D. W., Porritt, M. J., Wong, J. Y., Batchelor, P. E., Kalnins, R., Hughes, A. J., et al. (2000). Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. *Exp. Neurol.* 166, 127–135. doi: 10.1006/exnr.2000.7483

Hughes, A. J., Daniel, S. E., Kilford, L., and Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry* 55, 181–184. doi: 10.1136/jnnp.55.3.181

Hyman, C., Hofer, M., Barde, Y. A., Juhasz, M., Yancopoulos, G. D., Squinto, S. P., et al. (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* 350, 230–232. doi: 10.1038/350230a0

Jahanshahi, M., Jones, C. R., Zijlmans, J., Katzenschlager, R., Lee, L., Quinn, N., et al. (2010). Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. *Brain* 133, 727–745. doi: 10.1093/brain/awq012

Jiménez-Jiménez, F. J., Alonso-Navarro, H., García-Martín, E., and Agúndez, J. A. (2014). Cerebrospinal fluid biochemical studies in patients with Parkinson's disease: toward a potential search for biomarkers for this disease. *Front. Cell. Neurosci.* 8:369. doi: 10.3389/fncel.2014.00369

Karamohamed, S., Latourelle, J. C., Racette, B. A., Perlmutter, J. S., Wooten, G. F., Lew, M., et al. (2005). BDNF genetic variants are associated with onset age of familial parkinson disease: gene PD Study. *Neurology* 65, 1823–1825. doi: 10.1212/01.wnl.0000187075.81589.fd

Koponen, E., Võikar, V., Riekki, R., Saarelainen, T., Rauramaa, T., Rauvala, H., et al. (2004). Transgenic mice overexpressing the full-length neurotrophin receptor trkB exhibit increased activation of the trkB-PLCgamma pathway, reduced anxiety and facilitated learning. *Mol. Cell. Neurosci.* 26, 166–181. doi: 10.1016/j.mcn.2004.01.006

Koven, N. S., and Collins, L. R. (2014). Urinary brain-derived neurotrophic factor as a biomarker of executive functioning. *Neuropsychobiology* 69, 227–234. doi: 10.1159/000362242

Lawton, M. P., and Brody, E. M. (1969). Assessment of older people; self-maintaining and instrumental activity of daily living. *Gerontologist* 9, 179–186. doi: 10.1093/geront/9.3_part_1.179

Leal, G., Afonso, P. M., Salazar, I. L., and Duarte, C. B. (2014). Regulation of hippocampal synaptic plasticity by BDNF. *Brain Res.* 1621, 82–101. doi: 10.1016/j.brainres.2014.10.019

Leentjens, A. F., Dujardin, K., Marsh, L., Martinez-Martin, P., Richard, I. H., Starkstein, S. E., et al. (2008). Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. *Mov. Disord.* 23, 2004–2014. doi: 10.1002/mds.22229

Leverenz, J. B., Watson, G. S., Shofer, J., Zabetian, C. P., Zhang, J., and Montine, T. J. (2011). Cerebrospinal fluid biomarkers and cognitive performance in non-demented patients with Parkinson's disease. *Parkinsonism Relat. Disord.* 17, 61–64. doi: 10.1016/j.parkreldis.2010.10.003

Li, M., Dai, F. R., Du, X. P., Yang, Q. D., Zhang, X., and Chen, Y. (2012). Infusion of BDNF into the nucleus accumbens of aged rats improves cognition and structural synaptic plasticity through PI3K-ILK-Akt signaling. *Behav. Brain Res.* 231, 146–153. doi: 10.1016/j.bbr.2012.03.010

Lindenbach, D., and Bishop, C. (2013). Critical involvement of the motor cortex in the pathophysiology and treatment of Parkinson's disease. *Neurosci. Biobehav. Rev.* 37, 2737–2750. doi: 10.1016/j.neubiorev.2013.09.008

Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., et al. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society Task force guidelines. *Mov. Disord.* 27, 349–356. doi: 10.1002/mds.24893

Lu, W., Zhang, C., Yi, Z., Li, Z., Wu, Z., and Fang, Y. (2012). Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naïve patients with schizophrenia. *J. Mol. Neurosci.* 47, 505–510. doi: 10.1007/s12031-012-9750-4

MacDonald, P. A., and Monchi, O. (2011). Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. *Parkinsons Dis.* 2011:572743. doi: 10.4061/2011/572743

Marin, R. S., Biedrzycki, R. C., and Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Res.* 38, 143–162. doi: 10.1016/0165-1781(91)90040-v

Monaco, M., Costa, A., Caltagirone, C., and Carlesimo, G. A. (2013). Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an italian adult population. *Neurol. Sci.* 34, 749–754. doi: 10.1007/s10072-012-1130-x

Monteggia, L. M., Barrot, M., Powell, C. M., Berton, O., Galanis, V., Gemelli, T., et al. (2004). Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proc. Natl. Acad. Sci. U S A* 101, 10827–10832. doi: 10.1073/pnas.0402141101

Murer, M. G., Yan, Q., and Raisman-Vozari, R. (2001). Brain-derived neurotrophic factor in the control human brain and in Alzheimer's disease and Parkinson's disease. *Prog. Neurobiol.* 63, 71–124. doi: 10.1016/s0301-0082(00)00014-9

Nocentini, U., Di Vincenzo, S., Panella, M., Pasqualetti, P., and Caltagirone, C. (2002). La valutazione delle funzioni esecutive nella pratica neuropsicologica; dal modified card sorting test al modified card sorting test-roma version. Dati di standardizzazione. *Nuova Riv. di Neurol.* 12, 13–24.

Pålhagen, S., Qi, H., Mårtensson, B., Wålinder, J., Granérus, A. K., and Svenningsson, P. (2010). Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression. *J. Neurol.* 257, 524–532. doi: 10.1007/s00415-009-5353-6

Rana, A. Q., Ahmed, U. S., Chaudry, Z. M., and Vasan, S. (2015). Parkinson's disease: a review of non-motor symptoms. *Expert. Rev. Neurother.* 15, 549–562. doi: 10.1586/14737175.2015.1038244

Robbins, T. W., and Cools, R. (2014). Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. *Mov. Disord.* 29, 597–607. doi: 10.1002/mds.25853

Salehi, Z., and Mashayekhi, F. (2009). Brain-derived neurotrophic factor concentrations in the cerebrospinal fluid of patients with Parkinson's disease. *J. Clin. Neurosci.* 16, 90–93. doi: 10.1016/j.jocn.2008.03.010

Savitz, J., Solms, M., and Ramesar, R. (2006). The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav.* 5, 311–328. doi: 10.1111/j.1601-183x.2005.00163.x

Scalzo, P., Kümmer, A., Bretas, T. L., Cardoso, F., and Teixeira, A. L. (2010). Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. *J. Neurol.* 257, 540–545. doi: 10.1007/s00415-009-5357-2

Stacy, M. (2011). Nonmotor symptoms in Parkinson's disease. *Int. J. Neurosci.* 121(Suppl. 2), 9–17. doi: 10.3109/00207454.2011.620196

Svetel, M., Pekmezovic, T., Markovic, V., Novaković, I., Dobričić, V., Djuric, G., et al. (2013). No association between brain-derived neurotrophic factor G196A polymorphism and clinical features of parkinson's disease. *Eur. Neurol.* 70, 257–262. doi: 10.1159/000352033

Tükel, R., Gürvit, H., Ozata, B., Oztürk, N., Ertekin, B. A., Ertekin, E., et al. (2012). Brain-derived neurotrophic factor gene Val66Met polymorphism and cognitive function in obsessive compulsive disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159, 850–858. doi: 10.1002/ajmg.b.32092

Visser, M., Verbaan, D., van Rooden, S., Marinus, J., van Hilten, J., and Stiggelbout, A. (2009). A longitudinal evaluation of health-related quality of life of patients with Parkinson's disease. *Value Health* 12, 392–396. doi: 10.1111/j.1524-4733.2008.00430.x

Wilson, B. A., Evans, J. J., Emslie, H., Alderman, N., and Burgess, P. (1998). The development of an ecologically valid test for assessing patients with a dysexecutive syndrome. *Neuropsychol. Rehab.* 8, 213–228. doi: 10.1080/713755570

Woo, N. H., and Lu, B. (2006). Regulation of cortical interneurons by neurotrophins: from development to cognitive disorders. *Neuroscientist* 12, 43–56. doi: 10.1177/1073858405284360

Yeterian, E. H., and Pandya, D. N. (1991). Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. *J. Comp. Neurol.* 312, 43–67. doi: 10.1002/cne.903120105

Ziebell, M., Khalid, U., Klein, A. B., Aznar, S., Thomsen, G., Jensen, P., et al. (2012). Striatal dopamine transporter binding correlates with serum BDNF levels in patients with striatal dopaminergic neurodegeneration. *Neurobiol. Aging* 33, 428.e1–428.e5. doi: 10.1016/j.neurobiolaging.2010.11.010

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 16 June 2015
doi: 10.3389/fnbeh.2015.00151

Optimal hemodynamic response model for functional near-infrared spectroscopy

Muhammad A. Kamran, Myung Yung Jeong and Malik M. N. Mannan*

Department of Cogno-Mechatronics Engineering, Pusan National University, Busan, Korea

Functional near-infrared spectroscopy (fNIRS) is an emerging non-invasive brain imaging technique and measures brain activities by means of near-infrared light of 650–950 nm wavelengths. The cortical hemodynamic response (HR) differs in attributes at different brain regions and on repetition of trials, even if the experimental paradigm is kept exactly the same. Therefore, an HR model that can estimate such variations in the response is the objective of this research. The canonical hemodynamic response function (cHRF) is modeled by two Gamma functions with six unknown parameters (four of them to model the shape and other two to scale and baseline respectively). The HRF model is supposed to be a linear combination of HRF, baseline, and physiological noises (amplitudes and frequencies of physiological noises are supposed to be unknown). An objective function is developed as a square of the residuals with constraints on 12 free parameters. The formulated problem is solved by using an iterative optimization algorithm to estimate the unknown parameters in the model. Inter-subject variations in HRF and physiological noises have been estimated for better cortical functional maps. The accuracy of the algorithm has been verified using 10 real and 15 simulated data sets. Ten healthy subjects participated in the experiment and their HRF for finger-tapping tasks have been estimated and analyzed. The statistical significance of the estimated activity strength parameters has been verified by employing statistical analysis (i.e., t-value > t_{critical} and p-value < 0.05).

Keywords: hemodynamic response model, physiological noises, functional near-infrared spectroscopy, optimization algorithm, brain imaging

OPEN ACCESS

Edited by:
Katiuscia Sacco, University of Turin, Italy

Reviewed by:
Alicia Izquierdo, University of California, Los Angeles, USA
Mamiko Koshiba, Saitama Medical University, Japan

****Correspondence:***
Myung Yung Jeong, Department of Cogno-Mechatronics Engineering, Pusan National University, San 30 Jangjeon-dong Geumjeong-gu, Busan 609-735, Korea
myjeong@pusan.ac.kr

Received: *07 April 2015*
Accepted: *23 May 2015*
Published: *16 June 2015*

Citation:
Kamran MA, Jeong MY and Mannan MMN (2015) Optimal hemodynamic response model for functional near-infrared spectroscopy. Front. Behav. Neurosci. 9:151. doi: 10.3389/fnbeh.2015.00151

Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive and an emerging neuro-imaging technique (Santosa et al., 2013, 2014). The brain functional information is decoded through the interpretation of the variation in the optical properties of near-infrared (NIR) light (Naseer et al., 2014). NIRS monitors regional cerebral blood flow (rCBF) variations through the absorption changes of the NIR light at wavelengths between 650–950 nm. The oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) are two major chromospheres in the blood which absorb NIR light (Cope and Delpy, 1988). The concentration of HbO and HbR varies in the capillary blood during the rest and task sessions (Hu et al., 2013). Thus, brain functional information can be revealed by the estimation of HbO and HbR. fNIRS, with the ability to estimate both chromospheres, is a potential brain imaging modality (Kamran and Hong, 2014). Functional-magnetic resonance imaging (fMRI) (Cohen et al., 2014; Zhou et al., 2014) and electro-encephalography (EEG) are most frequently used cortical imaging modalities in past. In comparison, the huge size of fMRI and its paramagnetic constraints and low spatial resolution of EEG (Soekadar et al., 2014) enhance the potential position of fNIRS with good temporal resolution applicable to brain-computer interface (BCI) applications (Hu et al., 2010). Its spatial resolution is affected by the low penetration depth but lies in between fMRI and EEG (Boudriay et al., 2014). In addition to these attributes, its portability, safety and low cost features makes it on top position for rehabilitation and BCI applications (Khan et al., 2014).

The detection of neuronal activation in a particular cortical area refers to find out a specific waveform in the hemodynamic response (HR) (Ciftçi et al., 2008). In hemodynamic related neuro-imaging modality, likewise fNIRS, the existence of such waveform is indicated as a statistical comparison to a specific time series shape, known as canonical hemodynamic response function (cHRF) (Abdelnour and Huppert, 2009). The cHRF has a key role in the analysis of fNIRS time series as its shape varies between different brain regions, repetition of trials, and among subjects as well (Hong and Nugyen, 2014). The difference in the dynamic shape of HRF during event-related motor and visual paradigms revealed that the peak times of HbO, HbR, and total hemoglobin (HbT) for visual paradigm are approximately equal unlike for motor paradigm (Jasdzewski et al., 2003). Additionally, it is found that the wavelength dependent differential path length factor (DPF) and age can also affect the characteristics of HR (Duncan et al., 1996). A mismatch between these features could result as a decrease in the detection performance (Ciftçi et al., 2008).

The most commonly used model for cHRF is composed of two gamma functions to characterize the shape and undershoot, respectively. It has been frequently be implemented in the analysis of fMRI temporal data. The performance accuracy of detection is improved by modifying the basis set, incorporating temporal derivative (TD) and dispersion derivation (DD) along with blood oxygen level dependent (BOLD) in the design matrix (Friston et al., 1998). Thus, modeled HR is represented as a linear combination of three waveforms. The characteristics of BOLD response are similar to cHRF used in NIRS data analysis. But fNIRS signal has additional challenge of temporal correlation present in the optical signal caused by physiological noises (Hu et al., 2010). The feature values for basis set were imposed constraints (time-to-peak, number of positive and negative peaks, time to- and magnitude of undershoot) to improve the extraction of the specific wave-pattern that formulate the dynamic shape of cHRF (Ciftçi et al., 2008). Finally, a general linear model (GLM) framework is being utilized to tune the unknown parameters in the model using Bayesian approach (Ciftçi et al., 2008). A new public statistical toolbox (NIRS-SPM freely available at http://bispl.weebly.com/nirs-spm.html#/) for the analysis of NIRS data was introduced in 2009, incorporating GLM based estimation of the cortical activity (Ye et al., 2009). NIRS-SPM is an extension of statistical parameter mapping toolbox for fMRI, thus it uses the GLM approach with basis set (Friston et al., 1998) to map the neuronal activities on brain templates. A detailed comparison of modeling techniques for HRF in fMRI regarding assumptions in the models, the complexity in their design and interpretation shows that it is difficult to accurately recover true task-evoked changes (Lindquist et al., 2009). In their study, the gradient approach has been utilized for the estimation of the free parameters that define the shapes of different HRF models. The fNIRS time series is contaminated with physiological noises. Thus, addition of physiological signals in the design matrix could improve the detection of task-related HR and its application to BCI (Abdelnour and Huppert, 2009). The parameters of cHRF were assumed to be fixed in Abdelnour and Huppert (2009) and activity strength parameters have been estimated using Kalman filters. The conventional averaging techniques have been used most frequently in past but its major drawback is the number of trials necessary to derive the stable HRF (Scarpa et al., 2010). Scarpa et al. (2013) proposed the methodology of near/closed channels to remove the physiological noises with fix parameters to extract cHRF. Several studies in past have presented the idea of combining HR model and adaptive signal processing algorithms to recursively tune the model parameters (Kamran and Hong, 2013; Santosa et al., 2013; Hong and Nugyen, 2014). Thus, an optimal HR model is still a topic of interest for many researchers in fNIRS area.

In this paper, an optimal HR model has been proposed for the analysis of fNIRS time series. The measured HR is modeled as a linear combination of evoked-HR, the physiological noises (cardiac pulsation, respiratory beat and low frequency Mayer waves) and base-line correction. The evoked-HR is the convolution of cHRF and the experimental paradigm. The cHRF has been modeled as a linear combination of two gamma functions (Lindquist et al., 2009). Six parameters in the cHRF model have been supposed as free parameters (delay of response relative to onset, delay of undershoot, dispersion of response, dispersion of undershoot, baseline, and a scaling factor) (Friston et al., 1994). The selection of optimal parameters in cHRF is the crucial step due to the variability of HR in different brain regions, repetition of trials and among subjects as well. In addition, the variation in the frequency and amplitudes of the physiological noises is a common phenomenon in the optical signal (Abdelnour and Huppert, 2009). Thus, these parameters in physiological noises are also supposed as free. The optimal parameters whose subsequent results best fit to the measured HR are found through an iterative optimization process. Initial values for these free parameters have been used from existing literature (Friston et al., 1994; Abdelnour and Huppert, 2009). Finally, the brain-activation model is formulated as an optimization problem with 12 free parameters. The formulated pre-optimized model is passed to an iterative simplex method with initial parameter vector. The simplex algorithm (Spendley et al., 1962) and its modified version (Nelder and Mead, 1965) has frequently been used in past for many signal processing and engineering-design optimization applications (Luersen and Riche, 2004). Fifteen simulated data sets have been generated with known parameters to verify the correctness of the proposed algorithm. Simulated data sets have been generated through method described in Prince et al. (2003). A low error in the estimation of free parameters shows great potential of the proposed algorithm in this field. Ten healthy participants have been examined for motor related, typically box-car based rest-task-rest experiment. Finally, brain functional maps have been shown to localize the cortical activity.

Materials and Methods

Data Acquisition and Pre-Processing

Three different types of optical neuro-imaging systems are available commercially, namely, continuous wave (CW), frequency domain (FD), and time-resolved spectroscopy (Hu et al., 2012; Schudlo et al., 2013). CW is the least expensive and most frequently used approach for BCI applications. It provides the relative change in the concentration of HbO and HbR. The CW-NIRS imaging system (DYNOT: Dynamic Near-infrared Optical Tomography; NIRx Medical Technologies, Brooklyn, NY) was used in this study with two wavelengths of NIR light (760 and 830 nm). It has 32 optodes which can be configured as emitters or detectors according to the experimental requirement with data acquisition frequency of 1.81 Hz. The optodes were placed on the left motor cortex at 16 different emitter–detector–pair locations. The source–detector separation was approximately 3 cm. The optode configuration has been shown in **Figure 1A**.

The optical density variations measured through NIRS imaging system is converted into relative concentration changes of HbO and HbR using modified-Beer Lambert law (MBLL). According to MBLL, the optical densities at two different wavelengths can be solved by simple algebra to estimate the relative concentration changes of HbO and HbR with assumption of constant scattering (Power et al., 2011; Kamran and Hong, 2013)

$$\Delta HbO^i(k) = \frac{(\varepsilon_{HbR}^{\lambda_1}\frac{\Delta OD^{\lambda_2}(k)}{DPF^{\lambda_2}}) - (\varepsilon_{HbR}^{\lambda_2}\frac{\Delta OD^{\lambda_1}(k)}{DPF^{\lambda_1}})}{l^i(\varepsilon_{HbR}^{\lambda_1}\varepsilon_{HbO}^{\lambda_2} - \varepsilon_{HbR}^{\lambda_2}\varepsilon_{HbO}^{\lambda_1})}, \qquad (1)$$

$$\Delta HbR^i(k) = \frac{(\varepsilon_{HbO}^{\lambda_2}\frac{\Delta OD^{\lambda_1}(k)}{DPF^{\lambda_1}}) - (\varepsilon_{HbO}^{\lambda_1}\frac{\Delta OD^{\lambda_2}(k)}{DPF^{\lambda_2}})}{l^i(\varepsilon_{HbR}^{\lambda_1}\varepsilon_{HbO}^{\lambda_2} - \varepsilon_{HbR}^{\lambda_2}\varepsilon_{HbO}^{\lambda_1})}, \qquad (2)$$

where $\Delta HbO^i(k)$ and $\Delta HbR^i(k)$ are relative concentration changes of HbO and HbR, respectively, k is the discrete time, i represents the ith-channel of emitter-detector pair, λ_1 and λ_2 represent 760 and 830 nm wavelengths, $\varepsilon_{HbO}^{\lambda_1}$, $\varepsilon_{HbR}^{\lambda_1}$, $\varepsilon_{HbO}^{\lambda_2}$, and $\varepsilon_{HbR}^{\lambda_2}$ indicates the extinction coefficients (refers to the measure of absorption of light) of HbO and HbR at two different wavelengths, respectively, $\Delta OD^{\lambda_j}(k)$ is the optical density variation at kth-sample time at particular wavelength (j = 1, 2), l^i is the source-detector separation and DPF^{λ_j} is the DPF at particular wavelength (j = 1, 2). The extinction coefficients corresponding to 760 nm are 1.486 (for HbO) and 3.843 (for HbR) and those corresponding to 830 nm are 2.231 (for HbO) and 1.791 (for HbR) (Kamran and Hong, 2014).

Experimental Setup and Paradigm

Ten right-handed healthy subjects (age: 28 ± 7 years) participated in this study. None of the subject has the neuronal-disorder history before the experimentation. The written consent of each participant was collected before experimentation. The experiment was in accordance with the latest version of the Declaration of Helsinki. The subjects were completely introduced about the experiment and instrument before the start of the experimentation. The subjects were advised to avoid the head motion as much as possible. The load of NIRS optode fibers were supported through the hanger available with the instrument. The experiment includes a typical box-car rest-task-rest session. The experiment includes an initial rest of 10 s followed by a task session of 10 s and 30 s of a rest at the end. The subjects were instructed to tap their right index finger during task. A monitor screen was placed in front of the subject at a distance of approximately 110 cm. It remained blank during rest sessions and showed "finger tapping" during task session. The experimental paradigm has been shown in **Figure 1B**.

Simulated Subjects Data

The proposed algorithm is based upon an iterative optimization algorithm. Thus, it is necessary to verify the algorithm through simulated data sets with known values of free parameters. The simulated data is generated and supposed to be combination of HRF, three physiological signals, baseline term and random Gaussian noise. Fifteen different simulated data sets were generated using different values of free parameters. The data set has been generated with the methods described in existing literature (Prince et al., 2003; Abdelnour and Huppert, 2009)

$$HRF(k) = h(k) * u(k), \qquad (3)$$

$$h(k) = \left[\frac{k^{\alpha_1-1}\beta_1^{\alpha_1}e^{-\beta_1 k}}{\Gamma(\alpha_1)} - \frac{k^{\alpha_2-1}\beta_2^{\alpha_2}e^{-\beta_2 k}}{6\Gamma(\alpha_2)}\right] \qquad (4)$$

where u is the experimental paradigm, h is the cHRF, α_1 is the delay of the response, α_2 is the delay of the undershoot, β_1 is the dispersion of the response, β_2 is the dispersion of the undershoot and Γ represents the Gamma distribution. The physiological signals in simulated data have been generated through the linear combination of three sinusoids (Abdelnour and Huppert, 2009; Kamran and Hong, 2014). The specific values of free parameters used for all 15 data sets have been listed in **Table 1.**

Linear Brain Model and Parameter Optimization

GLM is a statistical linear model to decompose the output into predefined regressors. The existence of a particular regressor of interest depends upon the intensity of the activity strength parameter (Santosa et al., 2013). The positive value of the activity strength parameter with increasing t-value shows the significant existence of the particular regressor in the measured waveform (Hu et al., 2010). In this study, the measured HbO concentration change is supposed to be the linear combination of evoked-HRF, physiological noises and base-line correction

$$y^i_{HbO}(k) = a_o + a_1 HRF(k) + a_c \sin(2\pi f_c k) + a_r \sin(2\pi f_r k) + a_m \sin(2\pi f_m k) + \varepsilon^i(k), \qquad (5)$$

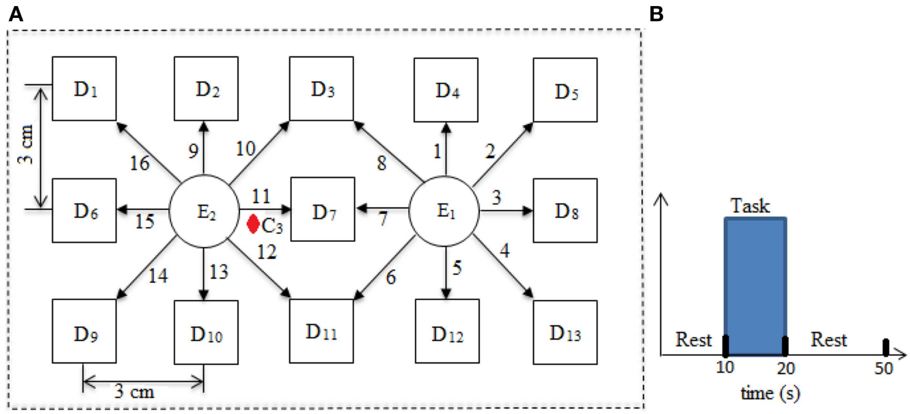


FIGURE 1 | Source/detector locations and distribution of channels (A) and experimental paradigm (B).

TABLE 1 | The results of 15 simulated data-sets: the actual values of parameters (A) and estimated ones through the proposed algorithm (E).

Sub.	A/E	a_c	f_c	a_r	f_r	a_m	f_m	α_1	α_2	β_1	β_2	a_0	a_1
1	A	1	1	1	0.2	1	0.07	6	16	1	1	14	10
	E	1.44	0.81	0.90	0.24	0.72	0.01	6.01	15.97	1.00	0.99	13.99	10.07
2	A	1.1	0.9	1.2	0.3	1.1	0.09	7	15	0.8	0.7	12	8
	E	1.59	0.79	1.74	0.007	0.71	0.018	9.23	16.38	0.98	1.5	13.5	4.40
3	A	1.2	0.95	1.3	0.22	1.2	0.08	3	12	0.9	1.1	12	6
	E	0.85	1.33	1.75	0.25	1.49	0.009	2.99	11.63	0.90	1.06	12.00	6.14
4	A	0.9	1.1	1	0.24	0.9	0.07	8	7	1	1	9	7
	E	1.42	1.22	0.85	0.29	1.73	.009	8.40	15.56	1.02	0.03	7.50	6.99
5	A	0.8	1	1.3	0.25	0.8	0.06	5	11	0.7	1.1	12	5
	E	1.05	1.10	1.44	0.22	0.01	0.009	5.34	8.75	0.77	0.99	11.98	5.16
6	A	0.7	0.9	0.9	0.25	0.7	0.05	9	18	0.9	1.3	14	9
	E	1.32	1.05	1.12	0.06	0.11	0.01	8.96	18.24	0.89	1.31	14.00	9.034
7	A	0.5	0.95	0.7	0.29	0.6	0.06	3	8	0.6	0.2	12	9
	E	0.96	1.3	1.20	0.24	1.68	0.01	2.99	8.23	0.60	0.20	11.99	9.03
8	A	0.4	1.1	0.6	0.3	0.5	0.07	4	18	1	1	8	5
	E	0.37	0.74	1.53	0.27	0.60	0.02	4.00	18.18	1.00	1.00	7.99	5.06
9	A	0.2	0.9	1	0.2	0.3	0.08	6	16	0.6	1.2	7	4
	E	1.99	1.29	0.23	0.23	1.51	0.01	4.93	6.70	0.57	1.35	6.95	4.50
10	A	1.2	0.9	1.2	0.23	1	0.09	5.5	17	0.8	1.4	11	3
	E	0.93	0.91	0.77	0.23	0.78	0.01	5.50	16.98	0.80	1.39	10.99	3.00
11	A	1.2	0.8	1	0.24	1.1	0.02	7	12	1.1	1.2	15	5
	E	0.48	1.40	1.18	0.11	1.78	0.01	8.91	7.01	1.53	0.04	12.72	2.05
12	A	1.1	0.85	0.9	0.26	0.8	0.03	4	10	1	0.8	11	7
	E	1.59	0.60	1.89	0.27	0.28	0.01	3.99	9.92	1.00	0.78	11.00	6.94
13	A	0.6	1.2	0.8	0.28	0.9	0.07	8	12	1.3	1	9	4
	E	1.98	0.88	0.50	0.17	0.89	0.01	7.99	11.63	1.30	0.96	8.99	4.04
14	A	0.4	0.8	0.9	0.20	0.6	0.08	9	12	0.5	0.3	10	3
	E	1.81	1.49	0.68	0.02	1.55	0.09	9.99	15.39	0.58	1.02	11.44	2.71
15	A	0.9	0.7	1.1	0.25	1	0.06	7	18	0.7	1.5	12	5
	E	1.36	1.05	1.36	0.11	1.09	0.01	6.55	15.44	0.69	0.02	9.95	5.60

where y^i_{HbO} is the measured HbO time series at ith-channel, a_o is the baseline, a_1 is the activity strength parameter, a_c, a_r, a_m, f_c, f_r, f_m are the amplitudes and the frequencies of the cardiac, respiratory and Mayer wave respectively and $\varepsilon^i(k)$ is the zero mean Gaussian noise at kth-sample time. Let us define a cost function J as sum of squares of residuals

$$J = \sum_{k=1}^{N}\{y^i_{HbO}(k) - (a_o + a_1 HRF(k) + a_c \sin(2\pi f_c k) + a_r \sin(2\pi f_r k) + a_m \sin(2\pi f_m k))\}^2. \quad (6)$$

The above cost function can be formulated in an optimization environment with constraints

$$\begin{array}{ll} \min\ J(\alpha_1,\alpha_2,\beta_1,\beta_2,a_o,a_1,a_c,a_m,a_r,f_c,f_r,f_m)\ \ s.t & \\ C_1: 2 \le \alpha_1 \le 10, & C_7: 0 \le a_c \le 2, \\ C_2: 6 \le \alpha_2 \le 20, & C_8: 0 \le a_r \le 2, \\ C_3: 0.5 \le \beta_1 \le 2, & C_9: 0 \le a_m \le 2, \\ C_4: 0 \le \beta_2 \le 1.5, & C_{10}: 0.5 \le f_c \le 1.5, \\ C_5: 0 \le a_o \le 20, & C_{11}: 0.2 \le f_r \le 0.3, \\ C_6: 0 \le a_1 \le 15. & C_{12}: 0.09 \le f_m \le 0.1. \end{array} \quad (7)$$

The optimal values of free parameters $(\alpha^*_1, \alpha^*_2, \beta^*_1, \beta^*_2, a^*_o, a^*_1, a^*_c, a^*_m, a^*_r, f^*_c, f^*_r, f^*_m)$ are estimated by improved version of simplex method [later named as Nelder–Mead simplex method (NMSM)]. The iteration of NMSM can be performed by three steps, namely, ordering, centroid and transformation. The simplex of size a is defined at initial point (Haftka et al., 1990)

$$x_j = x_o + pe_j + \sum_{\substack{k=1 \\ k\neq j}}^{n} qe_k;\ \ j = 1, 2, \ldots, n, \quad (8)$$

$$p = \frac{a}{n\sqrt{2}}(\sqrt{n+1} + n - 1)\ \&\ \ q = \frac{a}{n\sqrt{2}}(\sqrt{n+1} - 1). \quad (9)$$

where x_j ($j = 1, 2, .., n$) represent the vertices, x_o is the initial guess, $n = 12$ in this study and represents the number of free parameters, e_j represents the unit vector in the direction of jth vertex. The next step is to order the function in increasing order at all vertices and it is easy to sort as

$$J(x_l) < J(x_s) < J(x_h). \quad (10)$$

where x_l, x_h, and x_s, are the vertices with minimum value, maximum value and second highest value of the cost function, respectively. The next step is to discard the highest value by defining the centroid

$$\bar{x} = \frac{1}{n}\sum_{\substack{i=0 \\ i\neq h}}^{n} x_i, \quad (11)$$

where $\bar{x}$ is the centroid. The replacement of upper bound vertex of the cost function is done by reflection, expansion, contraction, and shrinkage (Lagarias et al., 1998). The mathematical equations for all these steps are given below

$$\text{Reflection}: x_r = \bar{x} + \delta_1(x_h - \bar{x}), \quad (12)$$

$$\text{Expansion}: x_e = \bar{x} + \delta_2(x_r - \bar{x}), \quad (13)$$

$$\text{Contraction}: x_c = \bar{x} + \delta_3(x_h - \bar{x}), \quad (14)$$

$$\text{Shrinkage}: x_e = \bar{x} + \delta_4(x_l - x_i);\ \ i = 0, 1, \ldots, n, \quad (15)$$

where δ_1, δ_2, δ_3, and δ_4 are coefficients of reflection, expansion, contraction, and shrinkage, respectively. The typical values of these coefficients have been chosen as 1, 2, 0.5, and 0.5, respectively (Lagarias et al., 1998; Luersen and Riche, 2004). The schematic of the algorithm is shown in **Figure 2**. The updated value at any step of iteration shall be replaced with bounded value, if it crosses bound at any step. The detail about the algorithm can be found in Haftka et al. (1990), Lagarias et al. (1998), and Luersen and Riche (2004).

Functional Brain Maps and Statistical Significance

The estimation of the cortical activation and its localization is a challenging task in the analysis of fNIRS data series. Previous studies showed that localization of the cortical activation could be statistically estimated by fitting the estimated HRF to a pre-defined HRF (Hu et al., 2010; Kamran and Hong, 2014; Santosa et al., 2014). Let the optimal brain activation model is

$$y^i_{HbO}(k) = a^*_0 + a^*_1 HRF^*(k) + a^*_c \sin(2\pi f^*_c k) + a^*_r \sin(2\pi f^*_r k) + a^*_m \sin(2\pi f^*_m k) + \varepsilon^i(k), \quad (16)$$

The estimated optimal value of the activity strength parameter, a_1, related to HRF indicates the activation of the particular brain region with proper statistics (Hu et al., 2010). The basic idea is to test whether the estimated value of the activity strength parameter is greater or less than a target value zero with statistically significance (t-value $> t_{\text{critical}}$ and p-value < 0.05). Thus, it is equivalent of testing a null hypothesis H_o with proper statistics i.e.,

$$H_o: a^*_1 = 0 \quad (17)$$

$$t_{value} = \frac{a^*_1 - 0}{SE(a^*_1)}. \quad (18)$$

where SE is the standard error of the estimated coefficient.

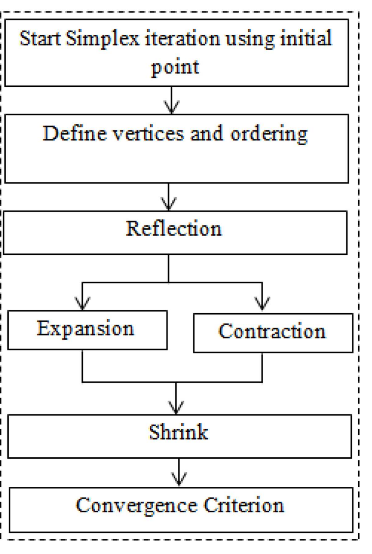


FIGURE 2 | Schematic of Nelder–Mead simplex method.

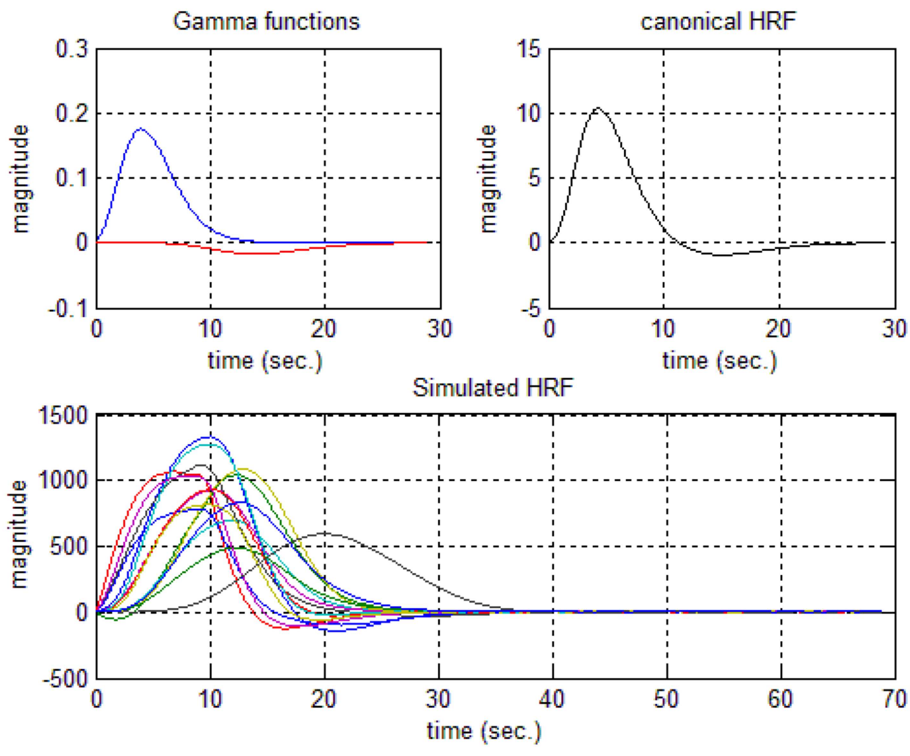


FIGURE 3 | Hemodynamic response function generations: two Gamma functions for generation of cHRF (top left), the standard cHRF (top right) and different simulated HRF (bottom).

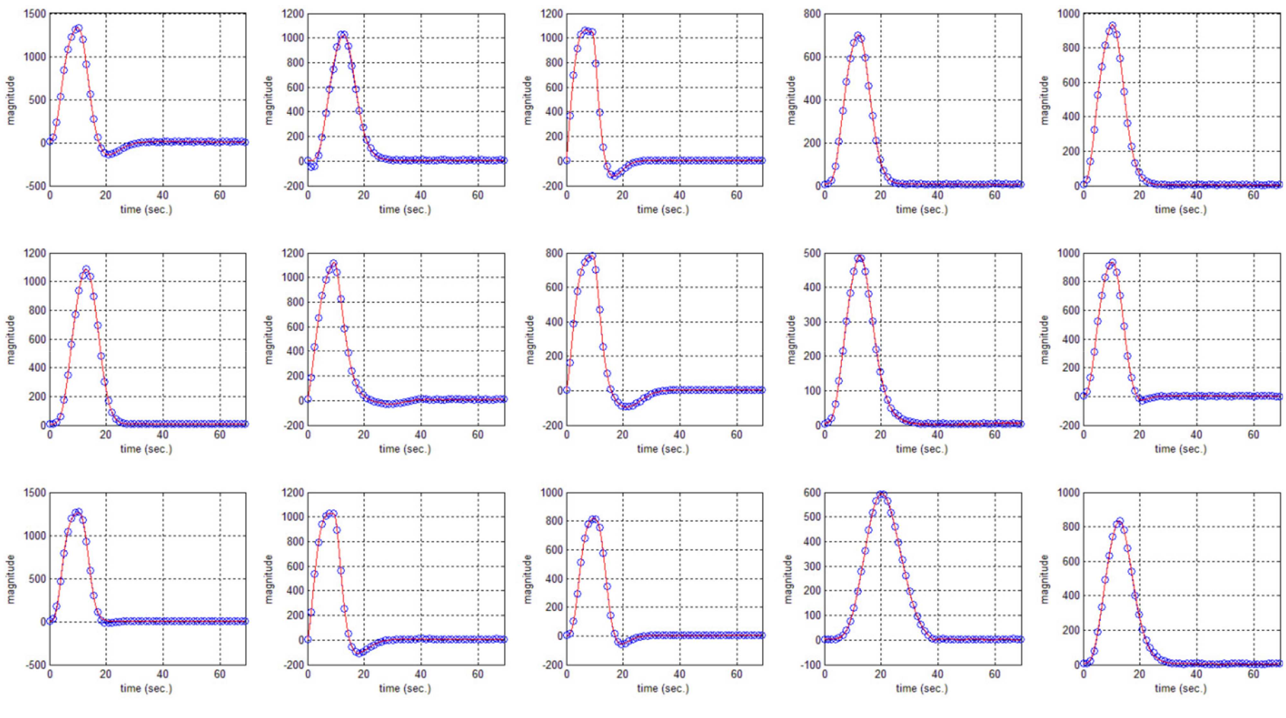


FIGURE 4 | HRF using actual values of free parameter (solid) and HRF using estimated values of free parameter (circular blue).

Results

In this study an online recursive optimization algorithm is proposed for cortical activation detection to display discrete brain maps. The algorithm is verified through 15 synthetic data sets and implemented to real data sets of 10 healthy subjects. The cHRF (**Figure 3**, top right panel) is modeled as two Gamma functions (**Figure 3**, top left panel). All the simulated data sets have been displayed in **Figure 3** (bottom panel). It is obvious to note that different width, height and undershoot have been considered for verifications. **Table 1** summarized the values of free parameters and their estimate through proposed algorithm. The comparison of HRF with actual parameter values and estimated parameter values has been shown in **Figure 4**. The results of the estimated-evoked-HR of 10 subjects have been presented in **Figure 5**. The significance of results has been verified using t-test. The t-maps of the cortical activations have been presented in **Figure 6**. **Figures 7**, **8** display a comparison of the estimated parameters related to most active channel in each subject of real data set and simulated data set, respectively.

Discussion

The non-invasive neuro-imaging techniques have a favorable position due to an increasing demand of BCI applications in the rehabilitation and medical diagnostics. There are several studies reported for the estimation of HRF in fMRI with numerical optimization techniques (Lindquist et al., 2009; Shah et al., 2014). But in the case of fNIRS, it constitutes an additional challenge of the physiological noise in the optical signal. Recently, several studies have been reported to analyze fNIRS time series using

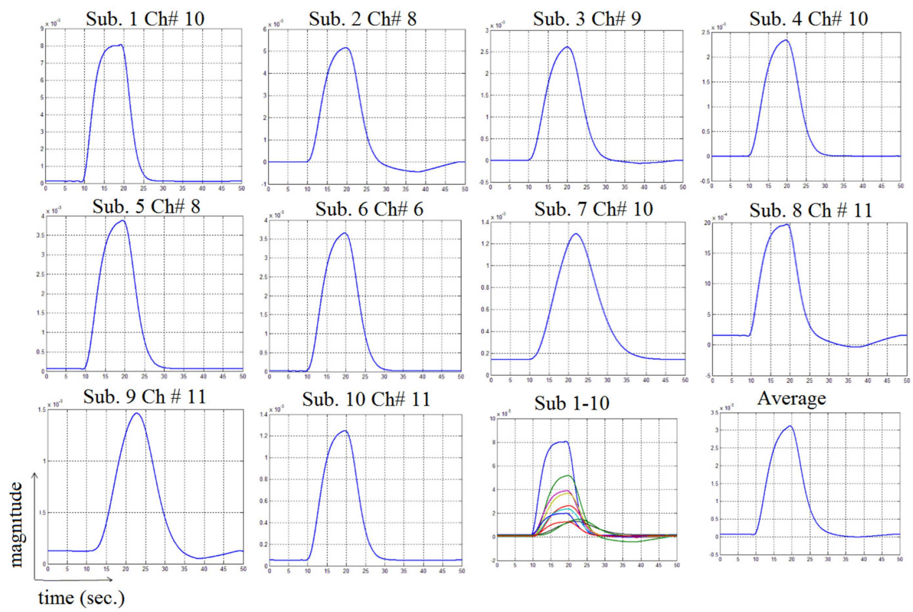


FIGURE 5 | Results of estimated HRF related to most active channel corresponding to all subjects.

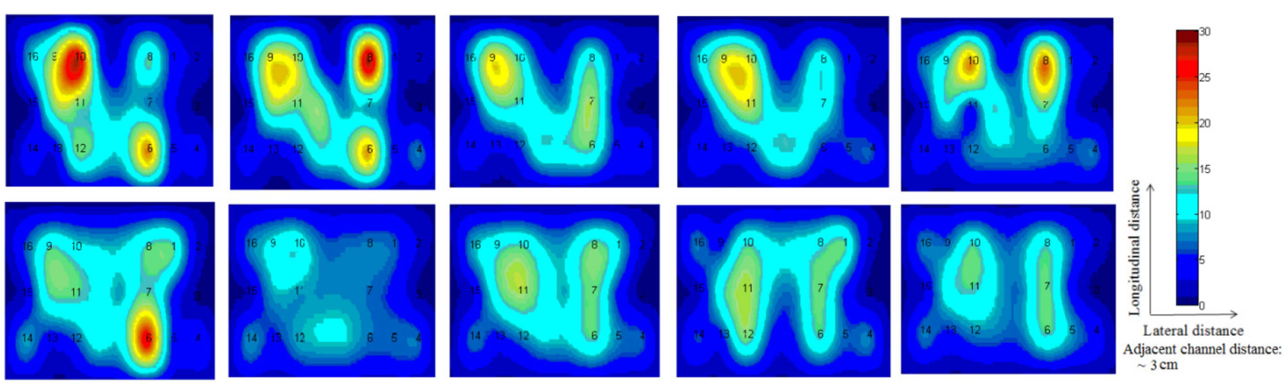


FIGURE 6 | *t*-Maps of each subject and all channels.

existing/new and/or modified versions of existing HRF models (Abdelnour and Huppert, 2009; Hu et al., 2010; Kamran and Hong, 2013, 2014; Santosa et al., 2013; Scarpa et al., 2013; Hong and Nugyen, 2014). The approaches vary in their implementation from simple estimation algorithms to more complex adaptive algorithms (Kamran and Hong, 2013) and blind signal processing (Santosa et al., 2013).

Hu et al. (2010) decomposed measured HRF into predefined regressors (evoked-HRF, base line correction and three others were included to design a set of high pass filter). Santosa et al. (2013) implemented the independent component analysis (ICA) framework to extract the statistically significance of a known wave pattern in the observed fNIRS data. Kamran and Hong (2013) explored the idea of adaptive signal processing to tune the variations in the measured HRF using parameter varying methodology. Later Kamran and Hong (2014) proposed to decompose HbO signal using ARMAX model for better cortical estimation as compared to existing ones. Abdelnour and Huppert (2009) proposed the adaptive framework to tune the HR with pre-built HRF in the model. Scarpa et al. (2013) emphases to remove the physiological noises by incorporating a near-detector (<0.7 cm from source) and to model the remaining

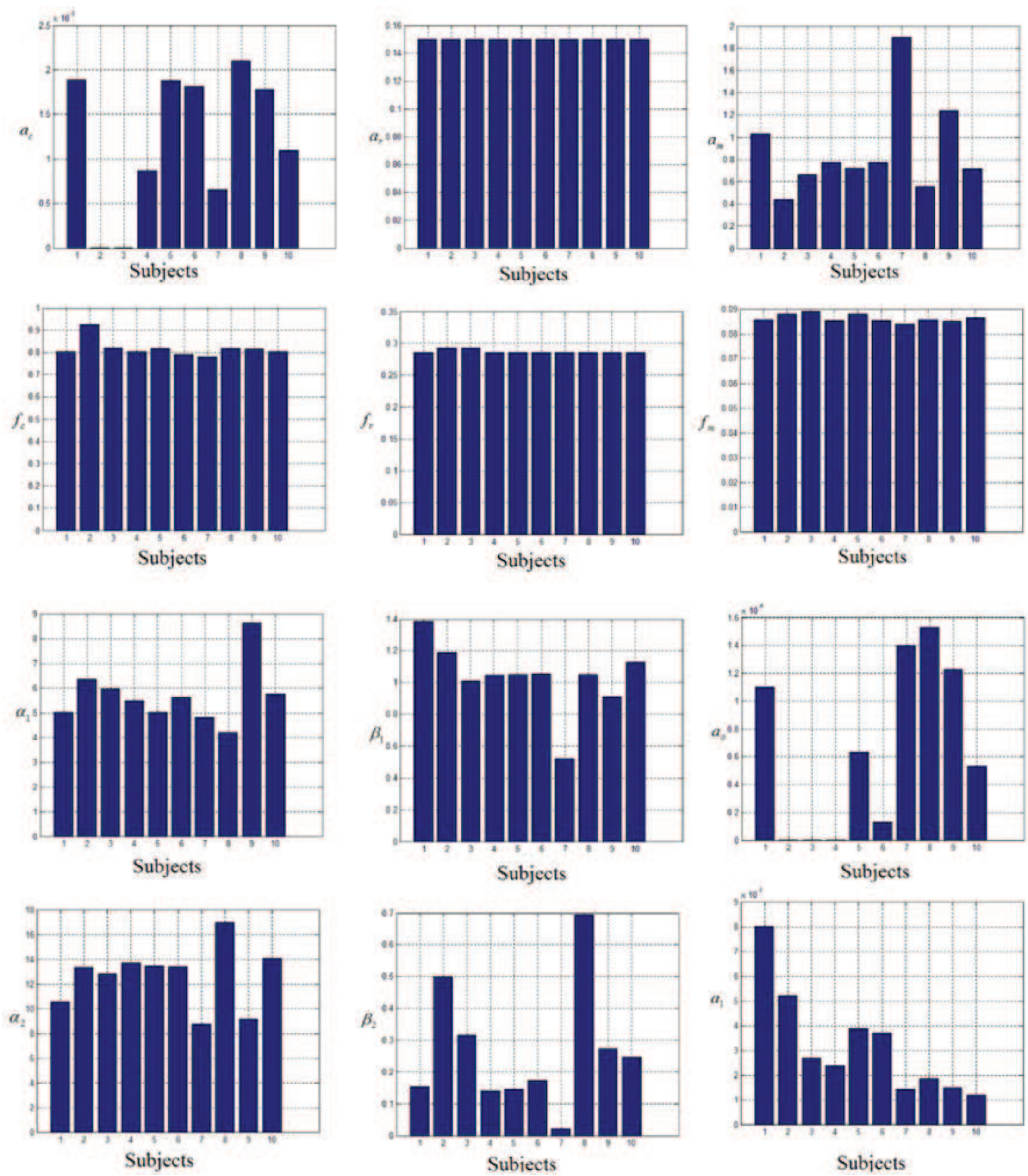


FIGURE 7 | Variations in the estimated parameters in real data sets.

signal as linear combination of pre-set evoked-HR and base line in Bayesian framework for adaptive tuning.

The DPF is a wavelength dependent factor and also varies with age of the subject causing variations in the hemodynamic signal (Duncan et al., 1996). Jasdzewski et al. (2003) reported that difference found in the characteristics of HRF in multiple brain regions. Their results suggest that the characteristics of HRF in different brain regions show variations. It is also observed in their study that some of the features like initial dip could be found in certain brain regions but not all. Hong and Nugyen (2014) developed a state-space model for different brain regions using adaptive signal processing framework. Their results revealed that there exist a significant difference between responses of different brain regions. It is a well-known fact that the hemodynamic signal has inter-subject variability as well as inter-trial variations. Hu et al. (2013) analyzed the reduction of trial-to-trial variations by analyzing correlation in the observed signal of different channels.

Thus existing literature suggest that the HR varies in its shape and characteristics not only in different brain areas, but it differs corresponding to the different mental task complexity, repetition, inter-subject and inter-trials as well. Some fNIRS-based BCI studies suggest that learning can improve the response, that is, less effort is required to repeat the same mental task. Thus, it is very important to model the HR in an adaptive framework together with a setup in which the parameters of HRF could be optimized as per real-time information in the measured response. Therefore, a recursive optimization algorithm have been presented in this study to model the variations in the HR. In contrast to existing fNIRS data analysis models, the proposed model has the capability to track time-varying characteristics (if exist) of HRF within same experiment as well. The estimation of

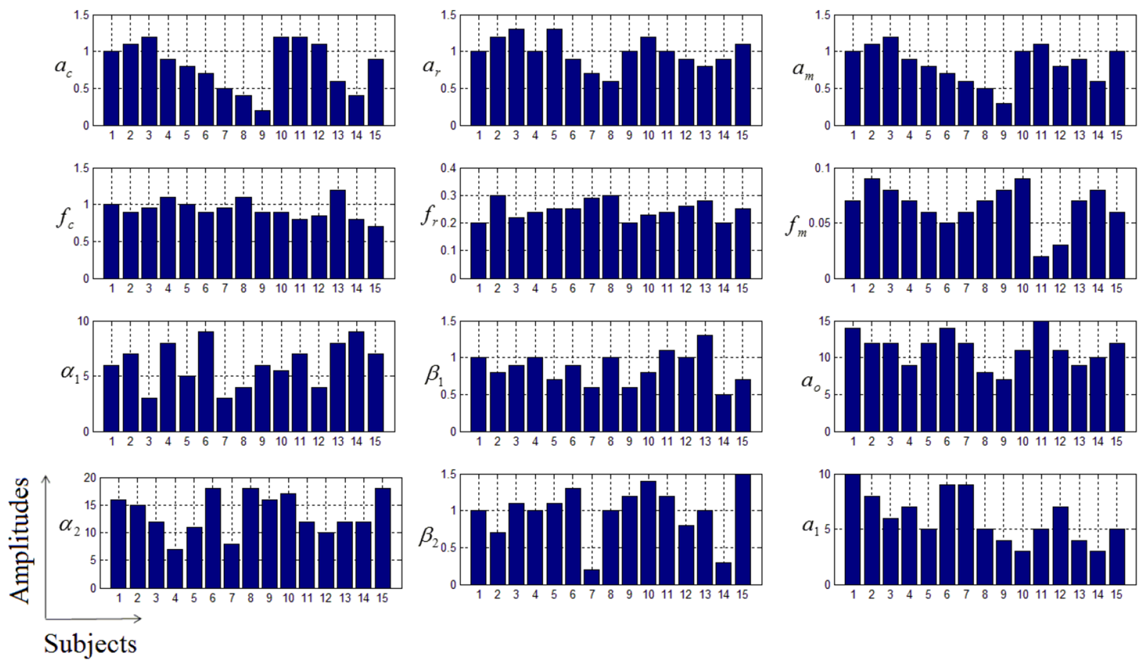


FIGURE 8 | Variations in the estimated parameters in simulated data sets.

TABLE 2 | The values of free parameter estimated through proposed algorithm in most active channel of each subject.

Sub.	a_c	f_c	a_r	f_r	a_m	f_m	α_1	α_2	β_1	β_2	a_0	a_1
1	0.00189	0.80311	0.15	0.28625	1.02993	0.08562	5.00065	10.5287	1.38593	0.15405	0.00011	8.02E-5
2	1.39E-10	0.92423	0.15	0.29274	0.44333	0.08792	6.35815	13.3583	1.19083	0.49997	5.41E-12	5.23E-5
3	7.57E-10	0.82143	0.15	0.29286	0.66165	0.08904	5.95863	12.8180	1.00771	0.31555	2.78E-13	2.69E-05
4	0.000866	0.803147	0.15	0.286365	0.775247	0.085313	5.497915	13.69872	1.044254	0.140721	6.68E-12	2.38E-05
5	0.0018793	0.815845	0.15	0.28643	0.72472	0.087949	5.020148	13.44807	1.051638	0.146827	6.34E-05	3.87E-05
6	0.0018195	0.790466	0.15	0.286283	0.773555	0.085377	5.63	13.39223	1.054951	0.172463	1.29E-05	3.71E-05
7	0.0006532	0.778724	0.15	0.286524	1.900005	0.08407	4.811197	8.741103	0.521305	0.02237	0.00014	1.43E-05
8	0.0020988	0.816158	0.15	0.286284	0.560308	0.085565	4.190606	16.95479	1.050989	0.694504	0.000153	1.85E-05
9	0.0017808	0.815718	0.15	0.286434	1.245347	0.085161	8.609862	9.202103	0.910313	0.273311	0.000123	1.5E-05
10	0.001092	0.803117	0.15	0.286282	0.71349	0.086521	5.750496	14.08988	1.127646	0.245757	5.33E-05	1.21E-05

pre-defined parameters of simulated data is shown in **Table 1**. It is obvious to observe that the proposed model estimated these parameters with a significant accuracy. After the validation of the algorithm using simulated data set, the methodology is applied to real data set of 10 subjects. The optimized values of HRF model parameters for 10 subjects have been listed in **Table 2**. The *t*-maps of each subject and all channels have been presented in **Figure 6**. It is evident from **Figures 5**, **6** that inter-subject difference exist in HRF parameters. Generally, inter-subject variability is due to the individual's differences in anatomical factors likewise skull and cerebrospinal fluid (CSF) structure, vessels distributions and the ratios of the arteries and veins. Thus, some of the subjects have more activation as compared to others.

Conclusion

An optimal HR model has been proposed that can extract the shape and scale of the HRF in addition to the amplitudes and the frequencies of the physiological sinusoids. Twelve parameters in the HR model have been supposed free with bounded constraints. The problem is formulated as an optimization problem and solved through an iterative optimization framework. The algorithm is first verified through different simulated data sets with known values of free parameters. A low error in estimation shows the accuracy of the proposed methodology. Furthermore, the algorithm is implemented to real data sets of 10 healthy participants. The parameters in HRF while repeating same trials are found to be different. Thus, it shall be beneficial for fNIRS data analysis, as the proposed model can track the characteristics of changes in HRF and physiological noises.

Acknowledgments

This work was supported by a 2-Year Research Grant of Pusan National University.

References

Abdelnour, A. F., and Huppert, T. (2009). Real-time imaging of human brain function by near-infrared spectroscopy using an adaptive general linear model. *Neuroimage* 46, 133–143. doi: 10.1016/j.neuroimage.2009.01.033

Boudriay, Y., Feltane, A., and Besio, W. (2014). Significant improvement in one-dimensional cursor control using Laplacian electroencephalography over electroencephalography. *J. Neural Eng.* 11:035014. doi: 10.1088/1741-2560/11/3/035014

Ciftçi, K., Sankur, B., Kahya, Y. P., and Akin, A. (2008). Constraining the general linear model for sensible hemodynamic response function waveforms. *Med. Biol. Eng. Comput.* 46, 779–787. doi: 10.1007/s11517-008-0347-6

Cohen, O., Koppel, M., Malach, R., and Friedman, D. (2014). Controlling an avatar by thought using real-time fMRI. *J. Neural Eng.* 11:035006. doi: 10.1088/1741-2560/11/3/035006

Cope, M., and Delpy, D. T. (1988). System for long-term measurement of cerebral blood and tissue oxygenation on newborn-infants by near-infrared trans-illumination. *Med. Biol. Eng. Comput.* 26, 289–294. doi: 10.1007/BF02447083

Duncan, A., Meek, J. H., Clemence, M., Elwell, C. E., Fallon, P., Tyszczuk, L., et al. (1996). Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy. *Pediatr. Res.* 39, 889–894.

Friston, K. J., Fletcher, P., Joseph, O., Holmes, A., Rugg, M. D., and Tunner, R. (1998). Event-related fMRI: characterizing differential responces *NeuroImage* 7, 30–40.

Friston, K. J., Holmes, A. P., Worsley, J.-P., Frith, C. D., and Frackowiak, R. S. J. (1994). Statistical parameter maps in functional imaging: a general linear model approach. *Hum. Brain Mapp.* 2, 189–210. doi: 10.1002/hbm.460020402

Haftka, R. T., Gurdal, Z., and Kamat, M. P. (1990). *Element of Structural Optimization.* Dordrecht: Kluwer Academic Publisher. doi: 10.1007/978-94-015-7862-2

Hong, K.-S., and Nugyen, H.-D. (2014). State-space models of impulse hemodynamic responses over motor, somatosensory, and visual cortices. *Biomed. Opt. Express* 5, 1778–1798. doi: 10.1364/BOE.5.001778

Hu, X. S., Hong, K.-S., and Ge, S. S. (2012). fNIRS-based online deception decoding. *J. Neural Eng.* 9:026012. doi: 10.1088/1741-2560/9/2/026012

Hu, X. S., Hong, K.-S., and Ge, S. S. (2013). Reduction of trial-to-trial variability in functional near-infrared spectroscopy signals by accounting for resting-state functional connectivity. *J. Biomed. Opt.* 18:017003. doi: 10.1117/1.JBO.18.1.017003

Hu, X. S., Hong, K.-S., Ge, S. S., and Jeong, M. Y. (2010). Kalman estimator-and general linear model-based on-line brain activation mapping by near-infrared spectroscopy. *BioMed. Eng. Online* 9:82. doi: 10.1186/1475-925x-9-82

Jasdzewski, G., Starngman, G., Wanger, J., Kwong, K. K., Poldrack, R. A., and Boas, D. A. (2003). Differences in the hemodynamic response to event-related motor and visual paradigms as measured by near-infrared spectroscopy. *NeuroImage* 20, 479–488. doi: 10.1016/S1053-8119(03)00311-2

Kamran, M. A., and Hong, K.-S. (2013). Linear parameter-varying model and adaptive filtering technique for detecting neuronal activities: an fNIRS study. *J. Neural Eng.* 10:056002. doi: 10.1088/1741-2560/10/5/056002

Kamran, M. A., and Hong, K.-S. (2014). Reduction of physiological effects in fNIRS waveforms for efficient brain-state decoding. *Neurosci. Lett.* 580, 130–136. doi: 10.1016/j.neulet.2014.07.058

Khan, M. J., Hong, M. J., and Hong, K.-S. (2014). Decoding of four movement directions using hybrid NIRS-EEG brain-computer interface. *Front. Hum. Neurosci.* 8:244. doi: 10.3389/fnhum.2014.00244

Lagarias, J. C., Reeds, J. A., Wright, M. H., and Wright, P. E. (1998). Convergence properties of Nelder-Mead simplex method in low dimension. *SIAM J. Optim.* 9, 112–147. doi: 10.1137/S1052623496303470

Lindquist, A., Meng, L. J., Atlas, L. Y., and Wager, T. D. (2009). Modeling the hemodynamic response function in fMRI: efficiency, bias and mis-modeling. *NeuroImage* 45, 187–198. doi: 10.1016/j.neuroimage.2008.10.065

Luersen, M. A., and Riche, R. L. (2004). Globalized Nelder–Mead method for engineering optimization. *Comput. Struct.* 82, 2251–2260. doi: 10.1016/j.compstruc.2004.03.072

Naseer, N., Hong, M. J., and Hong, K.-S. (2014). Online binary decision decoding using functional near-infrared spectroscopy for the development of brain-computer interface. *Exp. Brain Res.* 232, 555–564. doi: 10.1007/s00221-013-3764-1

Nelder, J. A., and Mead, R. (1965). A simplex method for functional minimization. *J. Comput.* 7, 308–313. doi: 10.1093/comjnl/7.4.308

Power, S. D., Kushki, A., and Chau, T. (2011). Towards a system-paced near-infrared spectroscopy brain-computer interface: differentiating prefrontal activity due to mental arithmetic and mental singing from the no-control state. *J. Neural Eng.* 8:066004. doi: 10.1088/1741-2560/8/6/066004

Prince, S., Kolehmainen, V., Kaipio, J. P., Franceschini, M. A., Boas, D., and Arridge, S. R. (2003). Time series estimation of biological factors in optical diffusion tomography. *Phys. Med. Biol.* 48, 1491–1504. doi: 10.1088/0031-9155/48/11/301

Santosa, H., Hong, M. J., and Hong, K.-S. (2014). Lateralization of music processing with noises in the auditory cortex: an fNIRS study. *Front. Behav. Neurosci.* 8:418. doi: 10.3389/fnbeh.2014.00418

Santosa, H., Hong, M. J., Kim, S.-P., and Hong, K.-S. (2013). Noise reduction in functional near-infrared spectroscopy signals by independent component analysis. *Rev. Sci. Instrum.* 84:073106. doi: 10.1063/1.4812785

Scarpa, F., Brigadoi, S., Cutini, S., Scatturin, P., Zorzi, M., Dell'Acqua, R., et al. (2013). A reference-channel based methodology to improve estimation of event-related hemodynamic response from fNIRS measurements. *NeuroImage* 72, 106–119. doi: 10.1016/j.neuroimage.2013.01.021

Scarpa, F., Cutini, S., Scatturin, P., Dell'Acqua, R., and Sparacino, G. (2010). Bayesian filtering of human brain hemodynamic activity elicited by visual short-term maintenance recorded through functional near-infrared spectroscopy (fNIRS). *Opt. Express* 18, 26550–26568. doi: 10.1364/OE.18.026550

Schudlo, L. C., Power, S. D., and Chau, T. (2013). Dynamic topographical pattern classification of multichannel prefrontal NIRS signals. *J. Neural Eng.* 10:046018. doi: 10.1088/1741-2560/10/4/046018

Shah, Z. Y., Wright, M. J., Thompson, P. M., McMahon, K. L., Blokland, G. G., de Zubicaray, G. I., et al. (2014). Modeling of hemodynamic response function in block design fMRI studies. *J. Cereb. Blood Flow Metab.* 34, 316–324. doi: 10.1038/jcbfm.2013.200

Soekadar, S. R., Witkowski, M., Cossio, E. G., and Birbaumer, N., and Cohen, L. G. (2014). Learned EEG-based brain self-regulation of motor-related oscillations during application of trans-cranial electric brain stimulation: feasibility limitations. *Front. Behav. Neurosci.* 8:93. doi: 10.3389/fnbeh.2014.00093

Spendley, W., Hext, G. R., and Himsworth, F. R. (1962). Sequential application of simplex designs in optimization and evolutionary operation. *Technometrics* 4, 441–468. doi: 10.1080/00401706.1962.10490033

Ye, J. C., Tak, S., Jang, K. E., Jung, J., and Jang, J. (2009). NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. *Neuroimage* 44, 428–447. doi: 10.1016/j.neuroimage.2008.08.036

Zhou, Y., Li, S., Dunn, J., Li, H., Qin, W., Zhu, M., et al. (2014). The neural correlates of risk propensity in males and females using resting-state fMRI. *Front. Behav. Neurosci.* 8:2. doi: 10.3389/fnbeh.2014.00002

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 22 March 2016
doi: 10.3389/fnbeh.2016.00048

Rehabilitation of Communicative Abilities in Patients with a History of TBI: Behavioral Improvements and Cerebral Changes in Resting-State Activity

Katiuscia Sacco[1,2,3], Ilaria Gabbatore[4], Elisabetta Geda[1], Sergio Duca[3,5], Franco Cauda[3,5], Bruno G. Bara[2,3] and Francesca M. Bosco[2,3]*

[1] Imaging and Cerebral Plasticity Research Group, Department of Psychology, University of Turin, Turin, Italy, [2] Center for Cognitive Science, Department of Psychology, University of Turin, Turin, Italy, [3] Neuroscience Institute of Turin, University of Turin, Turin, Italy, [4] Faculty of Humanities, Research Unit of Logopedics, Child Language Research Center, University of Oulu, Oulu, Finland, [5] GCS-fMRI, Koelliker Hospital, Department of Psychology, University of Turin, Turin, Italy

A targeted training program for the rehabilitation of communicative abilities—Cognitive Pragmatic Treatment (CPT)—has been developed and previously tested on a sample of patients with traumatic brain injury (TBI), whose performance was found to have improved. Since cortical plasticity has been recognized as the main mechanism of functional recovery, we investigated whether and how behavioral improvements following the training program are accompanied by brain modifications. Eight TBI patients took part in the training program and were behaviorally assessed pre- and post-treatment; six of these patients were also evaluated with pre- and post-treatment resting state (rs) functional magnetic resonance imaging (fMRI). At the end of the rehabilitation program patients showed improvement in overall communicative performance, in both comprehension and production tasks. A follow-up retest revealed the stability of these results 3 months after completing the training program. At the brain level, we found significant increases in the amplitude of low frequency fluctuation (ALFF) index in the bilateral precentral gyrus, in the right middle and superior temporal gyri, in the right cingulate gyrus, and in the left inferior parietal lobule. We discuss these differences of brain activity in terms of their possible contribution to promoting recovery.

Keywords: cognitive rehabilitation, communicative abilities, traumatic brain injury (TBI), functional magnetic resonance imaging (fMRI), cerebral plasticity

Edited by:
Nuno Sousa, University of Minho, Portugal

Reviewed by:
David Field, University of Reading, UK
Kathleen Pagulayan, VA Puget Sound Health Care System, USA

***Correspondence:**
Ilaria Gabbatore
ilaria.gabbatore@oulu.fi; ilariagabbatore@gmail.com

Received: *21 April 2015*
Accepted: *29 February 2016*
Published: *22 March 2016*

Citation:
Sacco K, Gabbatore I, Geda E, Duca S, Cauda F, Bara BG and Bosco FM (2016) Rehabilitation of Communicative Abilities in Patients with a History of TBI: Behavioral Improvements and Cerebral Changes in Resting-State Activity. Front. Behav. Neurosci. 10:48. doi: 10.3389/fnbeh.2016.00048

INTRODUCTION

Communication is a complex cognitive and social skill. It can be defined as the ability to comprehend and produce linguistic and extralinguistic acts, accompanied by paralinguistic expressions, appropriate with respect to discourse norms and social rules; moreover, within the conversation, topics have to be managed and turn-taking has to be respected (Bara, 2010). Such abilities can be impaired in certain neurological or psychiatric diseases: the assessment and rehabilitation of these functions require theoretically grounded and methodologically sound clinical protocols.

As far as the assessment of communicative abilities is concerned, we have developed the Assessment Battery for Communication (ABaCo; Sacco et al., 2008), for which normative data (Angeleri et al., 2012) and two equivalent forms (Bosco et al., 2012) are available. The ABaCo has been used in the assessment of children (Bosco et al., 2013), patients with schizophrenia (Colle et al., 2013), aphasia (Gabbatore et al., 2014), right brain lesion (Parola et al., 2016) and traumatic brain injury (TBI; Angeleri et al., 2008).

In order to rehabilitate patients whose communicative abilities have been impaired as a result of brain pathologies, we have developed the Cognitive Pragmatic Treatment (CPT; Gabbatore et al., 2015; Bosco et al., 2016). This clinical protocol derives its theoretical basis from Cognitive Pragmatics, a theory of the cognitive processes underlying human communication, according to which the essence of communication is to create meanings and share them with interlocutors, focusing on the interpretation of the intended meaning and going beyond the literal one (Bara, 2010). CPT is an integrated treatment, working on all aspects of communication: it gives patients the opportunity to test and train their ability to participate in communicative exchanges using words, gestures and prosodic cues, and to adhere to the conversational and social context of the communication. Moreover, the protocol works on self-awareness, theory of mind and planning abilities, which are essential aspects of effective communication (Coelho et al., 1995; Barkley et al., 2001; Champagne-Lavau et al., 2006). In our previous work (Gabbatore et al., 2015) we demonstrated the efficacy of CPT in the rehabilitation of a group of TBI patients. This result is of great importance because, as TBI patients often show specific pragmatic impairments that undermine the effectiveness and informativeness of communication (e.g., McDonald et al., 2000; Bara et al., 2001; Carlomagno et al., 2011; Coelho et al., 2013; Bosco et al., 2015), enhancing their communicative-pragmatic abilities can have a major impact on long-term outcome and social reintegration (Togher et al., 2014). Thus, it is essential to understand which neural mechanisms underlie the observed improvements in patients' communicative skills.

A rehabilitation training is based on the assumption that the brain is able to reorganize and relearn lost functions, i.e., the concept of neuronal plasticity. It is now widely recognized that the cerebral cortex of adult mammals is capable of widespread functional and structural plasticity: various studies highlighted that structural and functional modifications occur in the cerebral cortex after injury (for a review, see Nudo, 2011). Behavioral experience and brain injury interact; therefore it is reasonable that, after brain damage, targeted cognitive exercises are able to reshape the structure and function of uninjured areas of the brain, promoting recovery (for example, see Chen et al., 2010; Berlucchi, 2011). Neuroimaging methods allow the brain structures and functioning to be investigated; advanced techniques have shown promise in detecting macro- and microstructural activity-related changes in the brain (for a review, see Nordvik et al., 2014). Of the various functional imaging techniques, functional magnetic resonance imaging (fMRI) provides rehabilitation researchers with a non-invasive and reliable method for monitoring possible changes following therapeutic interventions. In the study of TBI patients, a whole brain perspective is fundamental in order to understand the mechanisms of recovery: indeed, TBI shifts brain function away from its normal organization, and this disruption is closely correlated with cognitive impairment (for a review, see for example, Strangman et al., 2005). Accordingly, neurological recovery requires changes at a brain level, re-establishing patterns of activity leading to the best possible behavior output.

Resting state (rs) fMRI paradigms explore brain activity when no task is being performed, and have the advantage of not being confounded by modifications in behavioral performance from before to after treatment. In the last years, rsfMRI studies have demonstrated that physical and cognitive training change resting-state activity (e.g., Sacco et al., 2009, 2011; Pieramico et al., 2012). Intrinsic brain activity is detected as low-frequency (<0.08 Hz) fluctuations (LFF) in blood-oxygenation level-dependent (BOLD) signals (Fox and Raichle, 2007). The amplitude of low frequency fluctuation (ALFF) can be used as an index reflecting regional intensity of resting state activity (Zang et al., 2007), and it has been associated with behavioral task performance (Zou et al., 2013). ALFF has been reported as a marker of brain function, able to characterize various abnormal conditions (examples of studies of neurological conditions are Li et al., 2014; Liu et al., 2014; Zhou et al., 2014). Besides, very recent studies assessed it as a way of evaluating brain plasticity (Yin et al., 2014; Lampit et al., 2015; Sacco et al., 2015). In the present work, we examined the functional plasticity of the ALFF index following the CPT training.

In line with Gabbatore et al. (2015), we predict a post-training increase of our chronic patients' communicative performance, as assessed through the equivalent forms of ABaCo (Bosco et al., 2012). At the neural level, in line with the previous literature (Yin et al., 2014; Lampit et al., 2015), we expect that behavioral improvements are accompanied by functional plastic changes in regions involved in the training: explorative imaging analysis should highlight what circuits support such changes.

MATERIALS AND METHODS

Participants

Eight adult patients with TBI participated in the study (3 females and 5 males) ranging in age from 23 to 50 years (M = 36.37 years; SD = 8.6 years); they ranged from 8 to 13 years of education (M = 9.12 years; SD = 1.81 years). TBI patients were recruited over a period of 1 year with the help of Centro Puzzle, a rehabilitation center for patients with brain injury, located in Turin.

The time after onset ranged from 1 to 16 years (M = 6.12; SD = 4.7). All of the patients were victims of severe TBI: the Glasgow Coma Scale in the acute phase was $\leq$8. Most of the patients had sustained their injury in a road traffic accident.

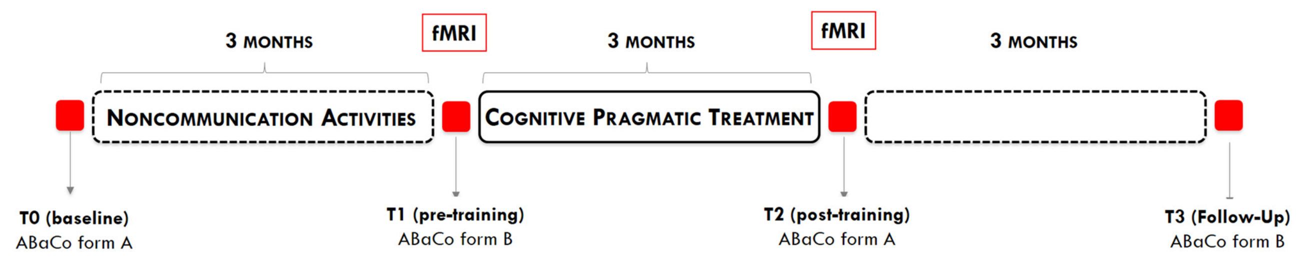


FIGURE 1 | Graphical representation of the experimental design.

At the time of the study, all the patients were in a post-acute phase; they were all living at home, even though none of them could manage to live independently without their partners or parents.

Inclusion criteria for the study were the following: the patients must have been (1) at least 18 years old; (2) at least in their 12th month after brain injury, in order to be sure that the cognitive profile was stable; (3) Italian native speakers; (4) in possession of linguistic skills, certified by the achievement of a cut-off score on the Token Test (De Renzi and Vignolo, 1962); cut off 29/36 on the Aachen Aphasia Test—denomination scale (AAT; Huber et al., 1983. Stanine cut-off score >6 which corresponds to absent or minimal deficit). In addition, they (5) had to demonstrate communicative-pragmatic deficits, evaluated through the administration of form A of the ABaCo (Bosco et al., 2012), in comparison to the normative performance of healthy persons on the ABaCo (Angeleri et al., 2012). Finally, (6) a minimum attendance rate of 60% at all rehabilitative sessions was mandatory to be included in this study. Exclusion criteria were: (1) prior history of TBI or other neurological disease; (2) neuropsychiatric illness; and (3) pre-morbid alcohol or drug addiction, evaluated on the basis of the anamnestic data from the case history of each patient, obtained through clinical interviews conducted by psychologists. All of the participants gave their written informed consent to participate in the research. Approval for the study had been obtained from the local ethics committee of the University of Turin, Comitato di Bioetica dell'Ateneo.

Experimental Design

The whole study lasted 9 months and included a 3-month training period and four assessment phases, designed according to an ABAB scheme (see **Figure 1**). Details regarding each assessment phase are provided in **Table 1**.

Cognitive Pragmatic Treatment: Structure and Procedure

The CPT program is made up of 24 sessions, each of which is concerned with improving one particular communication modality. Patients attend two sessions a week, for 12 weeks. Each session lasts about one and a half hours and includes a 10-min break. Patients worked in small groups of five under the supervision of a trained psychologist.

The treatment is primarily focused on improving patients' abilities to understand and produce the different expressive modalities of communication, i.e., linguistic, extralinguistic, paralinguistic, social appropriateness and conversational

TABLE 1 | Description of the assessment phases that made up the experimental design.

T0–Baseline	Three months before the treatment commenced, the recruited patients' communicative abilities were assessed using Form A of the Assessment Battery for Communication (ABaCo), in order to delineate their profile of communicative impairments and abilities. Following this assessment, the patients attended a number of sessions covering activities that were not specifically focused on communication. These sessions were held twice a week and lasted the same length of time as our Cognitive Pragmatic Training sessions. Such activities were used as a control procedure for improvements due to non-communicative activity and included: (a) memory and attention group and individual activities; (b) socializing activities, including group recreation and games activities; and (c) intellectual and creative activities, such as reading newspapers, cooking and painting. The aim of this control procedure was to detect any improvements in patients' communicative skills due to spontaneous recovery, as a consequence of unspecific activities or for the simple fact that they were taking part in a research program.
T1 – Pre-Training	Just a few days before the training program started, the patients' communicative performance was assessed again using Form B of the ABaCo, in order to obtain a measure of their abilities before the rehabilitation program and to verify the absence of any improvements due to attending unspecific activities between T0 and T1. Moreover, before the training program started, a resting state fMRI (rsfMRI) paradigm was administered to the patients, in order to investigate functional activity of the brain areas through the ALFF index.
T2 – Post-Training	Immediately after the end of the training program, Form A of the ABaCo was administered to the patients, in order to evaluate the efficacy of the treatment on their communicative performance. After the treatment, the patients underwent fMRI scanning once again, in order to evaluate any changes in terms of functional activity.
T3 – Follow-Up	Three months after the end of the rehabilitation program, Form B of the ABaCo was administered to the patients, in order to evaluate the stability of the improvements in their communicative abilities in time.

*The content of **Table 1** has been adapted from Gabbatore et al. (2015).*

abilities. Other sessions focus on additional aspects of communicative and cognitive competence such as awareness, theory of mind, and planning abilities.

The therapist helps the patients to use their communicative skills and teaches them how to deal with the problems they encounter in normal everyday communication contexts, using self-monitoring strategies and providing feedback in an ecological setting. Each session is video-recorded and video-feedback is provided during and at the end of the program. This allows the experimenters to give an analytical critical contribution to the contents of the sessions and helps patients to become aware of their difficulties and their progress from one session to the next.

The various training activities are designed to improve: (i) inferential abilities; (ii) use of extralinguistic; (iii) paralinguistic cues; and (iv) appropriateness respect to the social context (e.g., formal vs. informal). Since the linguistic aspects of communication are fairly well preserved in these patients, the exercises focus principally on communicative intentions. The therapist encourages patients to go beyond the literal meaning of an utterance and instead focus on the speaker's communicative intentions and the different meanings and implications depending on the circumstances and context, as for example in the production and comprehension of non-literal language, i.e., indirect communicative acts and irony. Special attention is given to training patients to combine linguistic utterances with the appropriate paralinguistic cues, such as tone of voice expressing a specific emotion or communicative intention, and extralinguistic aspects, as emotional facial expressions and body movements. Finally, patients are taught to modulate their communicative acts according to a particular social context. For patients with TBI, communicative inappropriateness represents one of the greatest obstacles to social reintegration. The topics covered during the CPT program and the overall structure of each session are described in Gabbatore et al. (2015).

Experimental Procedures

In order to test the effectiveness of the training program we administered the equivalent forms (Bosco et al., 2012) of the ABaCo, Giunti OS, Firenze (Sacco et al., 2008, 2013; Angeleri et al., 2012, 2015), pre- and post-training. Equivalent forms of ABaCo comprise four evaluation scales, i.e., linguistic, extra-linguistic, paralinguistic and context, for investigating the main pragmatic aspects of communication. These include direct and indirect communicative acts, deceits, irony, appropriateness to conversational and social aspects of communicative interactions. Each scale comprises a *comprehension* and a *production* subscale, designed to evaluate abilities in each of these areas. Tasks consist of *vis-à-vis* interactions between patient and examiner, comprehension of short videotapes showing communicative interactions, and production of specific communicative acts starting from a given context (for a more detailed description, see Bosco et al., 2012). Coding procedure was carried out by two trained, independent judges, who were not involved in the administration of the rehabilitative program. They watched the video-recorded experimental sessions and coded on specific score sheets. Scores range from 0 to 1: one point is given for each correct answer and the score for each scale is the mean of the scores obtained on tasks belonging to that particular scale. No points were awarded for incorrect answers. In comprehension tasks, patients were awarded one point if they understood the task correctly, and none if they did not. Likewise, in production tasks, patients were awarded one mark for producing an appropriate communication act and none if they failed to produce the requested communication act in the requested modality (for a detailed description of scoring criteria, see Bosco et al., 2013). ABaCo has shown excellent content and construct validity, as well as good reliability measures in terms of inter-rater reliability and internal consistency (Sacco et al., 2008, 2013); the two equivalent forms, when evaluated on a sample of TBI, showed excellent internal consistency (global score: $\alpha = 0.92$ in Form A and 0.95 in Form B) and between-form correlation (Pearson's correlation between the global scores of Form A and B: $r = 0.92$; Bosco et al., 2012). Normative data are also available (see Angeleri et al., 2012).

In addition to the behavioral assessment, patients underwent an fMRI scan before and after the treatment. In order to evaluate the presence of any differences in patients' neuronal activity before and after our rehabilitation program, we used a resting state paradigm (RS) for imaging data. We compared the results obtained in the pre- and post-treatment phases in order to establish whether any objective effects of the rehabilitation treatment on neuronal activity were detectable. Data acquisition was performed at the Koelliker Hospital in Turin. As well as the resting state scan (18 min), a set of anatomical MRI images were acquired (10 min). The exclusion criteria for this study consisted of having internal metal objects such as aneurysm and hemostatic clips, implanted electrodes and electrical devices such as pacemakers, orthopedic material and devices. Subjects suffering from anxiety disorders such as claustrophobia, panic attacks or any disorder which could be severely aggravated by confined spaces such as that of the MRI scan were also excluded. Of the eight patients who completed the training, as well as the pre- and post-training tests, six were also evaluated with fMRI.

The participants were instructed to lie on the scanner-bed and simply keep their eyes closed. They were asked not to think of anything in particular, and not to fall asleep. In case of an emergency, the patients could press a button in order to ask for help and, if necessary, interrupt the procedure at any time.

Data were acquired using a 1.5-T Philips Intera with a Sense high field high resolution head coil (MRIDC) optimized for functional imaging. Functional images (T2-weighted) were acquired using echoplanar sequences (EPI), with 3000 ms of repetition time (TR), 60 ms of echo time (TE) and a 90° flip angle. We used a 64×64 acquisition matrix; the FoV was 256 mm. The total acquisition set consisted of 500 volumes. Each volume comprised 19 axial slices, parallel to the anterior-

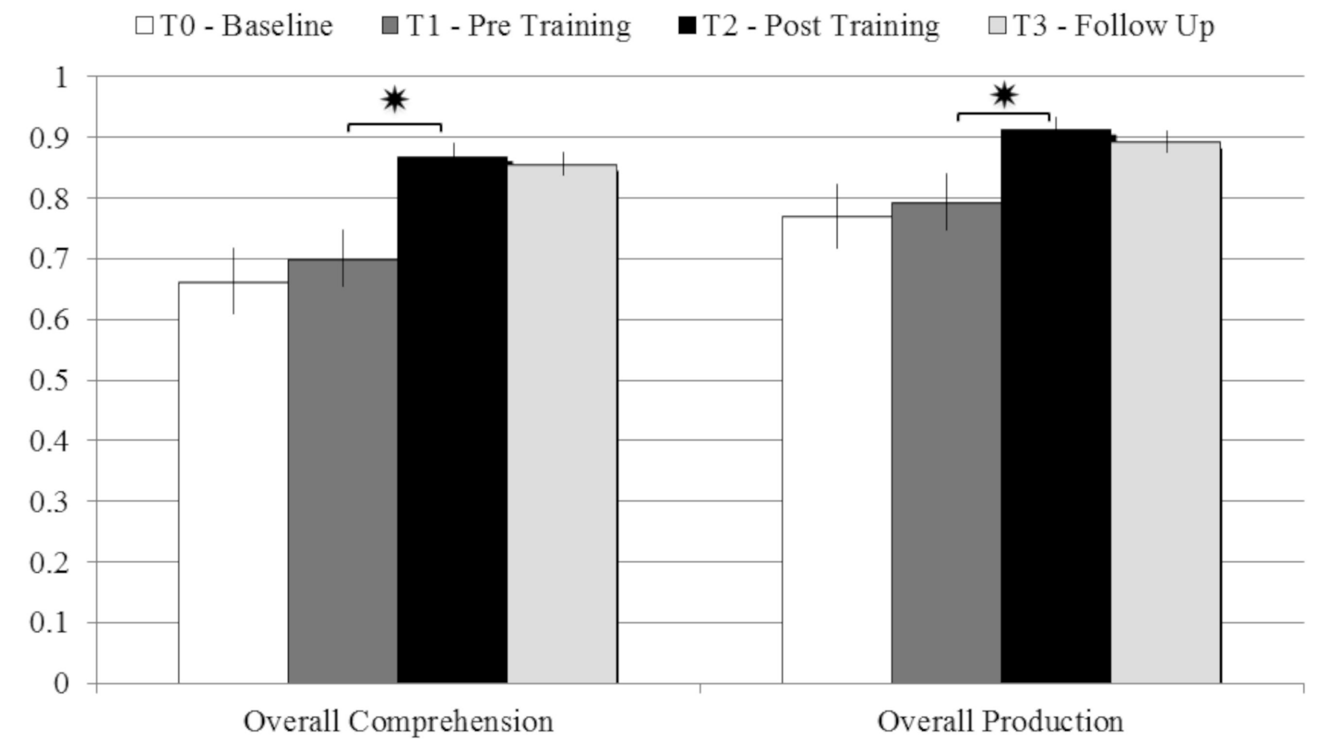


FIGURE 2 | Comparison between the average scores obtained in comprehension and production tasks at T0 – Baseline; T1 – pre Training; T2 – post Training; T3 – Follow-up, with error bars representing standard error. *$p < 0.05$.

posterior (AC–PC) commissure line and covering the whole brain; the slices were 5 mm thick with a 1 mm gap. Aiming at reaching a steady-state magnetization before acquisition of the actual experimental data, we added two scans at the beginning of the functional scan and we discarded their data. In the same session, for each participant we acquired a set of three-dimensional high-resolution structural images (T1-weighted). This data set was acquired using a Fast Field Echo (FFE) sequence, with a TR of 25 ms, the shortest TE and a 30° flip angle. For this acquisition we used a 256 × 256 acquisition matrix; the FoV was 256 mm. The set comprised 160 sagittal contiguous images covering the whole brain. The in-plane resolution was 1 mm × 1 mm and the slices were 1 mm thick (1 mm × 1 mm × 1 mm voxels).

RESULTS

Communicative-Pragmatic Assessment

In order to verify the efficacy of the training program we ran a paired-samples *T*-test analysis on patients' performance in the different evaluation phases. We found no improvement due to the unspecific control activities the patients attended between T0 (baseline) and T1 (pre-training), in either comprehension ($t = 0.74$; $p = 0.48$) or production ($t = 0.66$; $p = 0.53$).

On the other hand, patients' performance at T2 (post-training) was significantly better than at T1 (pre-training), in both comprehension (*T*-test: $t = 4.17$; $p = 0.004$; Cohen's $d = 1.65$) and production ($t = 2.85$; $p = 0.025$; $d = 1.042$). The improvements were stable even 3 months after the end of the rehabilitative program, as demonstrated by the comparison between patients' performance at T2 (post-training) and at the follow-up assessment, in both comprehension ($t = 0.3$; $p = 0.77$) and production ($t = 0.44$; $p = 0.67$; see **Figure 2**).

The fMRI data were analyzed using Brain Voyager QX software (Brain Innovation, Maastricht, Holland). The functional data of each subject were pre-processed as follows: (1) mean intensity adjustment in order to prevent global signal variability; (2) slice scan time correction, through the use of a sinc interpolation algorithm; (3) 3D motion correction: all the volumes were spatially aligned to the first volume by rigid body transformations, adopting a algorithm of trilinear interpolation; (4) spatial smoothing with a Gaussian kernel of 4 mm FWHM; and (5) temporal filters, i.e., linear and non-linear trend removal through the use of a temporal high-pass filter (frequency pass = 0.008 Hz), adopted to remove drifts due to scanner and other low frequency noises.

After pre-processing, the temporal series of each voxel were filtered using a band-pass filter ($0.01 < f < 0.08$ Hz) in order to remove both the very low frequencies and the noise due to high frequencies (respiratory and cardiac frequencies). The filtered time series was then transformed into a frequency

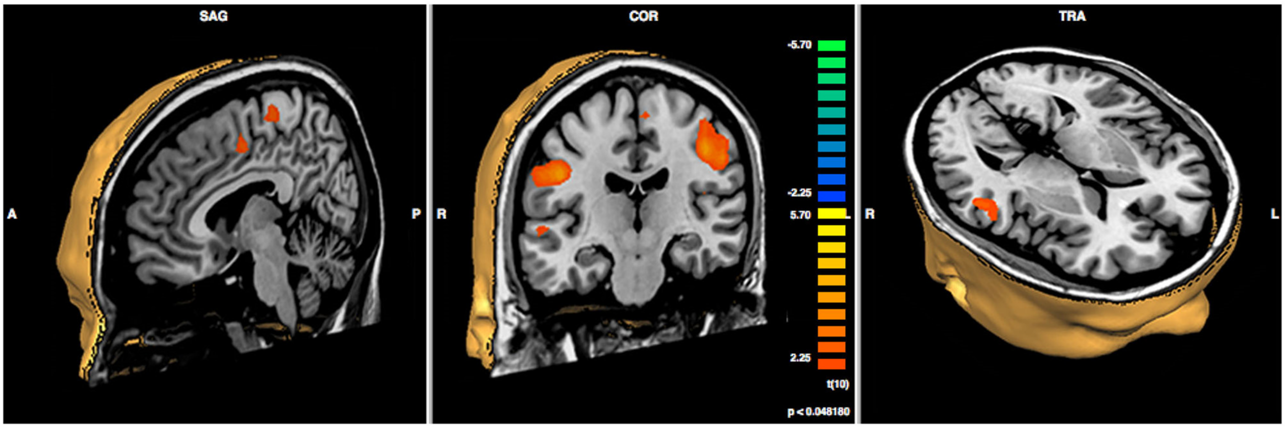


FIGURE 3 | Results of paired sample *t*-test post- minus pre-treatment within group ($N = 6$; $p < 0.048$).

TABLE 2 | Results of paired sample *t*-test post- minus pre-treatment within group.

Localization (Brodmann area)	Right hemisphere				Left hemisphere			
	t value	Talairach coordinates			*t* value	Talairach coordinates		
+ Middle temporal gyrus (22)	4.239	53	−32	3				
Superior temporal gyrus (22)		54	−28	4				
+ Precentral gyrus (6)	3.885	44	−11	33				
+ Cingulate gyrus (24)	3.393	2	1	45				
+ Inferior parietal lobule (7)					3.967	−31	−50	48
+ Precentral gyrus (4)					4.971	−40	−17	39

The table indicates the Talairach coordinates of local maxima of cortical structures showing significant ($p < 0.05$, corrected for multiple comparisons) activity. The "+" symbol in the first column indicates that all regions showed increased functional activity.

domain using Fourier transformation; this process allowed us to decompose a signal made up of several frequencies and identify the spectrum of the signal. The power spectrum represents the energy of the signal at different frequencies. We then calculated the ALFF index of the resting-state fMRI signal, a whole brain analysis that is based on the amplitude of the low frequency fluctuations of the rsfMRI signal and is interpreted as reflecting the intensity of the spontaneous regional activity of the brain. The ALFF Index was obtained by calculating the square root of the power spectrum between 0.01 and 0.08 Hz, and represents the average amplitude of the signal in a single voxel (Zou et al., 2008).

In order to compare pre- vs. post-treatment neuronal activations, a repeated measures *T*-test analysis was performed at $p < 0.05$; a false discovery rate (FDR) correction for multiple comparisons was applied (corrected $q = 0.05$; Benjamini et al., 2001). The script used for the analysis produces a specific output that is able to show the Brodmann areas and the cerebral gyri and sulci implicated in the changes. Specifically, we found significant increases in functional activity in the bilateral precentral gyrus, in the right middle and superior temporal gyri, in the right cingulate gyrus, and in the left inferior parietal lobule, see **Figure 3** and **Table 2**.

DISCUSSION

Many studies have demonstrated that, even after an injury, the brain is able to remodel itself thanks to its diffuse and redundant connectivity, as well as its ability to create new circuits through remapping (Silasi and Murphy, 2014). Given the incidence and the impact of TBI on cognitive abilities, understanding the mechanisms of plasticity in such patients is crucial in order to develop new approaches for promoting recovery. Spontaneous recovery of cognitive functioning only takes place within a critical period after injury: specifically, it has been reported that in cases of severe TBI, spontaneous reorganization occurs between 3 and 6 months post-injury (e.g., Strangman et al., 2005; Nakamura et al., 2009; Hillary et al., 2011); for a recent review of brain imaging studies revealing plasticity after TBI, See Kou and Iraji (2014). But what happens when this critical window has ended? Can patients improve their cognitive functioning even when their clinical conditions are chronic and have stabilized? Chronic recovery involves the renewal of functional brain networks, which can be targeted by prescribing specific rehabilitation programs (Muñoz-Cespedes et al., 2005). The effects of proactive neurorehabilitation, designed to address certain impaired domains in chronic TBI patients, have been investigated using fMRI predominantly for those networks with a well-understood brain topography, such as the motor (e.g., Sacco et al., 2011) and the language (e.g., Laatsch and Krisky, 2006) systems. Integrative functions that draw upon multiple higher-order processes have been less studied because of technical and methodological difficulties; however, these include some cognitive aspects that have a critical role in social and vocational reintegration. A recent clinical trial investigated abstract reasoning abilities mediated by the prefrontal cortex in mild and moderate chronic TBI (Krawczyk et al., 2013). Here, we showed that the improvement in communicative abilities is accompanied by an increase in functional activity which involves the bilateral precentral gyri, the right middle and superior temporal gyri, the right cingulate gyrus and the left inferior parietal lobule. Several data in the literature have demonstrated the role of these cerebral areas in pragmatic competence; more specifically, they seem to be involved in most of the processes addressed by the CPT.

First of all, the increased activity largely concerns the right hemisphere. Indeed, some authors (Kuperberg et al., 2000; Long and Baynes, 2002) investigated the functional architecture of linguistic abilities in the brain, showing that even though the left hemisphere is dominant in processing most of the language functions, the right hemisphere has a role in discourse representation and in processing narrative construction. Robertson et al. (2000) pointed out that the cognitive process of mapping during discourse comprehension resulted in a higher neural activity in the right than in the left hemisphere. In more detail, the authors reported higher levels of fMRI activation in the right middle temporal gyrus while participants read a set of unconnected sentences that they ordered into narratives. Taken together, these findings converge to indicate the right hemispheric regions are recruited when discourse processing requires the creation of connections between separate entities in the utterance, in order to compute plausibility or coherence or to make inferences (Eviatar and Just, 2006). In the right hemisphere, we found increased activity in the middle and superior temporal gyri and in the precentral gyrus, which have been related to figurative aspects of communication, i.e., metaphors and irony, requiring inferential ability (Wang et al., 2006). Eviatar and Just (2006) observed that ironic statements determined significantly higher activation levels than literal statements in the right superior and middle temporal gyri; according to these authors, the processing of irony might be related to the processing of communicative intent or the construction of a coherent narrative. Other studies have suggested that the precentral gyrus is involved in the comprehension of metaphoric sentences (Mashal et al., 2007). Besides their involvement in processing non-literal meaning, the above-mentioned regions have been related to emotional aspects of communicative interactions (i.e., paralinguistic ability trained in CPT). Mitchell et al. (2003) found that the normal response to emotional prosody was primarily mediated by the right-lateral temporal lobe, specifically the superior and middle temporal gyri. In particular, these areas were significantly activated despite the presence of semantic information and whether the individuals were either passively listening or actively attending to emotional prosody, i.e., comprehension and production of prosodic elements. In an fMRI study conducted by Ethofer et al. (2006), participants were asked to judge the content of emotional words to rate the valence of the affective prosody: the right middle temporal gyrus was shown to be specifically involved in processing affective prosody. These data are in line with previous studies showing that, in individuals with left temporal lobe damage, the ability to comprehend emotional prosody was largely unaffected, while in individuals with right temporal lobe damage this capacity could be severely impaired (Starkstein et al., 1994). Buchanan et al. (2000) found the right temporal region to be involved in the processing of prosodic aspects of the speech signal, while other neuroimaging studies (e.g., Glasser and Rilling, 2008) have suggested that, while the left superior and middle temporal gyri are involved in phonologic and lexical-semantic processing, the right middle temporal gyri and the precentral gyrus are involved in the prosodic production mechanism. The same regions have also been found to have a role in emotional facial expressions, i.e., the ability to read emotions and process information from the many changeable characteristics of a face (Taylor et al., 1998; Damasio et al., 2000; Phan et al., 2002; Batty and Taylor, 2003; Kuchinke et al., 2005), which is essential in structuring successful communicative interactions and is widely treated during CPT. As far as the cingulate gyrus is concerned, it has also been shown to be responsible for conflict-monitoring and outcome-evaluation (Botvinick, 2007; Torta and Cauda, 2011). Kuchinke et al. (2005) suggested that conflict, acting as an indicator of information-processing demands, drives reactive adjustments in cognitive control, and that the anterior cingulate cortex could have a role in this ability. Consistently, in the CPT, specific training sessions aimed to strengthen patients' sensitivity to contextual and social information by making them understand the social context and choose their behavior accordingly. Social appropriateness, indeed, significantly improved after training.

Taken as a whole, our results reveal a series of analogies with those of a meta-analysis (Rapp et al., 2012) examining fMRI studies on non-literal language, i.e., metaphors, proverbs, idioms, irony and sarcasm. The authors identified a common network for non-literal language, including the left and right inferior frontal gyrus, the left middle and superior temporal gyrus, with contributions from the medial prefrontal, superior frontal, cerebellar, parahippocampal, precentral and inferior parietal regions.

The present work can be seen as a first step towards the discovery of brain mechanisms underlying communication recovery in chronic TBI. Indeed, it presents some limitations, associated with sample size and heterogeneity. In particular, the number of patients who could undergo fMRI was small and this prevented us from the possibility of correlating the neuroimaging changes with the outcome measures. Future research is needed to assess and scan a greater number of patients: the correlation between brain networks and behavioral measures will be essential to reveal whether certain pre- and post-training patterns of functional activity are associated with better outcomes. This would help in administering the training program to those patients who can benefit most from its use; moreover, it would shed light onto the specific brain changes needed to significantly improve patients' performance. Finally, although the various characteristics present in our sample made it representative of the TBI population, which is heterogeneous by its nature, it would be interesting to understand whether and how age, gender, educational level and time from lesion onset affect the range of improvement.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

This study has been supported by Brain Imaging Group ONLUS and by local research funds (ex 60%) managed by University of Turin, Department of Psychology, year 2014. We are grateful to the reviewers, whose comments helped us greatly to improve the article.

REFERENCES

Angeleri, R., Bara, B. G., Bosco, F. M., Colle, L., and Sacco, K. (2015). *Batteria Per L'Assessment Della Comunicazione (ABaCO).* Firenze: Giunti OS Organizzazioni Speciali.

Angeleri, R., Bosco, F. M., Gabbatore, I., Bara, B. G., and Sacco, K. (2012). Assessment battery for communication (ABaCo): normative data. *Behav. Res. Methods* 44, 845–861. doi: 10.3758/s13428-011-0174-9

Angeleri, R., Bosco, F. M., Zettin, M., Sacco, K., Colle, L., and Bara, B. G. (2008). Communicative impairment in traumatic brain injury: a complete pragmatic assessment. *Brain Lang.* 107, 229–245. doi: 10.1016/j.bandl.2008.01.002

Bara, B. G. (2010). *Cognitive Pragmatics: The Mental Processes of Communication.* Cambridge, MA: MIT Press.

Bara, B. G., Cutica, I., and Tirassa, M. (2001). Neuropragmatics: extralinguistic communication after closed head injury. *Brain Lang.* 77, 72–94. doi: 10.1006/brln.2000.2430

Barkley, R. A., Edwards, G., Laneri, M., Fletcher, K., and Metevia, L. (2001). The efficacy of problem-solving communication training alone, behavior management training alone and their combination for parent-adolescent conflict in teenagers with ADHD and ODD. *J. Consult. Clin. Psychol.* 69, 926–941. doi: 10.1037/0022-006x.69.6.926

Batty, M., and Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Brain Res. Cogn. Brain Res.* 17, 613–620. doi: 10.1016/s0926-6410(03)00174-5

Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., and Golani, I. (2001). Controlling the false discovery rate in behavior genetics research. *Behav. Brain Res.* 125, 279–284. doi: 10.1016/s0166-4328(01)00297-2

Berlucchi, G. (2011). Brain plasticity and cognitive neurorehabilitation. *Neuropsychol. Rehabil.* 21, 560–578. doi: 10.1080/09602011.2011.573255

Bosco, F. M., Angeleri, R., Colle, L., Sacco, K., and Bara, B. G. (2013). Communicative abilities in children: an assessment through different phenomena and expressive means. *J. Child Lang.* 40, 741–778. doi: 10.1017/s0305000913000081

Bosco, F. M., Angeleri, R., Sacco, K., and Bara, B. G. (2015). Explaining pragmatic performance in traumatic brain injury: a process perspective on communicative errors. *Int. J. Lang. Commun. Disord.* 50, 63–83. doi: 10.1111/1460-6984.12114

Bosco, F. M., Angeleri, R., Zuffranieri, M., Bara, B. G., and Sacco, K. (2012). Assessment battery for communication: development of two equivalent forms. *J. Commun. Disord.* 45, 290–303. doi: 10.1016/j.jcomdis.2012.03.002

Bosco, F. M., Gabbatore, I., Gastaldo, L., and Sacco, K. (2016). Communicative-pragmatic treatment in schizophrenia: a pilot study. *Front. Psychol.* 7:166. doi: 10.3389/fpsyg.2016.00166

Botvinick, M. M. (2007). Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn. Affect. Behav. Neurosci.* 7, 356–366. doi: 10.3758/cabn.7.4.356

Buchanan, T. W., Lutz, K., Mirzazade, S., Specht, K., Shah, N. J., Zilles, K., et al. (2000). Recognition of emotional prosody and verbal components of spoken language: an fMRI study. *Cogn. Brain Res.* 9, 227–238. doi: 10.1016/s0926-6410(99)00060-9

Carlomagno, S., Giannotti, S., Vorano, L., and Marini, A. (2011). Discourse information content in non-aphasic adults with brain injury: a pilot study. *Brain Inj.* 25, 1010–1018. doi: 10.3109/02699052.2011.605097

Champagne-Lavau, M., Stip, E., and Joanette, Y. (2006). Social cognition deficit in schizophrenia: accounting for pragmatic deficits in communication abilities? *Curr. Psychiatry. Rev.* 2, 309–315. doi: 10.2174/157340006778018184

Chen, H., Epstein, J., and Stern, E. (2010). Neural plasticity after acquired brain injury: evidence from functional neuroimaging. *PM R* 2, S306–S312. doi: 10.1016/j.pmrj.2010.10.006

Coelho, C., Lê, K., Mozeiko, J., Hamilton, M., Tyler, E., Krueger, F., et al. (2013). Characterizing discourse deficits following penetrating head injury: a preliminary model. *Am. J. Speech Lang, Pathol.* 22, S438–S448. doi: 10.1044/1058-0360(2013/12-0076)

Coelho, C. A., Liles, B. Z., and Duffy, R. J. (1995). Impairments of discourse abilities and executive functions in traumatically brain-injured adults. *Brain Inj.* 9, 471–477. doi: 10.3109/02699059509008206

Colle, L., Angeleri, R., Vallana, M., Sacco, K., Bara, B. G., and Bosco, F. M. (2013). Understanding the communicative impairments in schizophrenia: a preliminary study. *J. Commun. Disord.* 46, 294–308. doi: 10.1016/j.jcomdis.2013.01.003

Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L. L., Parvizi, J., et al. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat. Neurosci.* 3, 1049–1056. doi: 10.1038/79871

De Renzi, E., and Vignolo, L. A. (1962). The token test: a sensitive test to detect receptive disturbances in aphasics. *Brain* 85, 665–678. doi: 10.1093/brain/85.4.665

Ethofer, T., Anders, S., Erb, M., Herbert, C., Wiethoff, S., Kissler, J., et al. (2006). Cerebral pathways in processing of affective prosody: a dynamic causal modeling study. *Neuroimage* 30, 580–587. doi: 10.1016/j.neuroimage.2005.09.059

Eviatar, Z., and Just, M. A. (2006). Brain correlates of discourse processing: an fMRI investigation of irony and conventional metaphor comprehension. *Neuropsychologia* 44, 2348–2359. doi: 10.1016/j.neuropsychologia.2006.05.007

Fox, M. D., and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711. doi: 10.1038/nrn2201

Gabbatore, I., Angeleri, R., Bosco, F. M., Cossa, F. M., Bara, B. G., and Sacco, K. (2014). Assessment of communicative abilities in aphasic patients. *Minerva Psichiatr.* 55, 45–55.

Gabbatore, I., Sacco, K., Angeleri, R., Zettin, M., Bara, B. G., and Bosco, F. M. (2015). Cognitive pragmatic treatment: a rehabilitative program for traumatic brain injury individuals. *J. Head Trauma Rehabil.* 30, E14–E28. doi: 10.1097/HTR.0000000000000087

Glasser, M. F., and Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cereb. Cortex* 18, 2471–2482. doi: 10.1093/cercor/bhn011

Hillary, F., Slocomb, J., Hills, E., Fitzpatrick, N., Medaglia, J., Wang, J., et al. (2011). Changes in resting connectivity during recovery from severe traumatic brain injury. *Int. J. Psychophysiol.* 82, 115–123. doi: 10.1016/j.ijpsycho.2011.03.011

Huber, W., Poeck, K., Weniger, D., and Willmes, K. (1983). *Der Aachener Aphasie Test (AAT).* Gottingen: Hogrefe.

Kou, Z., and Iraji, A. (2014). Imaging brain plasticity after trauma. *Neural Regen. Res.* 9, 693–700. doi: 10.4103/1673-5374.131568

Krawczyk, D. C., Marquez de la Plata, C., Schauer, G. F., Vas, A. K., Keebler, M., Tuthill, S., et al. (2013). Evaluating the effectiveness of reasoning training in military and civilian chronic traumatic brain injury patients: study protocol. *Trials* 14:29. doi: 10.1186/1745-6215-14-29

Kuchinke, L., Jacobs, A. M., Grubich, C., Võ, M. L., Conrad, M., and Herrmann, M. (2005). Incidental effects of emotional valence in single word processing: an fMRI study. *Neuroimage* 28, 1022–1032. doi: 10.1016/j.neuroimage.2005.06.050

Kuperberg, G. R., McGuire, P. K., Bullmore, E. T., Brammer, M., Rabe-Hesketh, S., Lythgoe, D., et al. (2000). Common and distinct neural substrates for pragmatic, semantic and syntactic processing of spoken sentences: an fMRI study. *J. Cogn. Neurosci.* 12, 321–341. doi: 10.1162/089892900562138

Laatsch, L., and Krisky, C. (2006). Changes in fMRI activation following rehabilitation of reading and visual processing deficits in subjects with traumatic brain injury. *Brain Inj.* 20, 1367–1375. doi: 10.1080/02699050600983743

Lampit, A., Hallock, H., Suo, C., Naismith, S. L., and Valenzuela, M. (2015). Cognitive training-induced short-term functional and long-term structural plastic change is related to gains in global cognition in healthy older adults: a pilot study. *Front. Aging Neurosci.* 7:14. doi: 10.3389/fnagi.2015.00014

Li, C., Liu, C., Yin, X., Yang, J., Gui, L., Wei, L., et al. (2014). Frequency-dependent changes in the amplitude of low-frequency fluctuations in subcortical ischemic vascular disease (SIVD): a resting-state fMRI study. *Behav. Brain Res.* 274, 205–210. doi: 10.1016/j.bbr.2014.08.019

Liu, X., Wang, S., Zhang, X., Wang, Z., Tian, X., and He, Y. (2014). Abnormal amplitude of low-frequency fluctuations of intrinsic brain activity in alzheimer's disease. *J. Alzheimers Dis.* 40, 387–397. doi: 10.3233/JAD-131322

Long, D. L., and Baynes, K. (2002). Discourse representation in the two cerebral hemispheres. *J. Cogn. Neurosci.* 14, 228–242. doi: 10.1162/089892902317236867

Mashal, N., Faust, M., Hendler, T., and Jung-Beeman, M. (2007). An fMRI investigation of the neural correlates underlying the processing of novel metaphoric expressions. *Brain Lang.* 100, 115–126. doi: 10.1016/j.bandl.2005.10.005

McDonald, S., Code, C., and Togher, L. (2000). *Communication Disorders Following Traumatic Brain Injury.* Hove: Psychology press.

Mitchell, R. L., Elliott, R., Barry, M., Cruttenden, A., and Woodruff, P. W. (2003). The neural response to emotional prosody, as revealed by functional magnetic resonance imaging. *Neuropsychologia* 41, 1410–1421. doi: 10.1016/s0028-3932(03)00017-4

Muñoz-Cespedes, J. M., Rios-Lago, M., Paul, N., and Maestu, F. (2005). Functional neuroimaging studies of cognitive recovery after acquired brain damage in adults. *Neuropsychol. Rev.* 15, 169–183. doi: 10.1007/s11065-005-9178-5

Nakamura, T., Hillary, F. G., and Biswal, B. B. (2009). Resting network plasticity following brain injury. *PLoS One* 4:e8220. doi: 10.1371/journal.pone.0008220

Nordvik, J. E., Walle, K. M., Nyberg, C. K., Fjell, A. M., Walhovd, K. B., Westlye, L. T., et al. (2014). Bridging the gap between clinical neuroscience and cognitive rehabilitation: the role of cognitive training, models of neuroplasticity and advanced neuroimaging in future brain injury rehabilitation. *NeuroRehabilitation* 34, 81–85. doi: 10.3233/NRE-131017

Nudo, R. J. (2011). Neural bases of recovery after brain injury. *J. Commun. Disord.* 44, 515–520. doi: 10.1016/j.jcomdis.2011.04.004

Parola, A., Gabbatore, I., Bosco, F. M., Bara, B. G., Cossa, F. M., Gindri, P., et al. (2016). Assessment of pragmatic impairment in right hemisphere damage. *J. Neurolinguistics* 39, 10–25. doi: 10.1016/j.jneuroling.2015.12.003

Phan, K. L., Wager, T., Taylor, S. F., and Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348. doi: 10.1006/nimg.2002.1087

Pieramico, V., Esposito, R., Sensi, F., Cilli, F., Mantini, D., Mattei, P. A., et al. (2012). Combination training in aging individuals modifies functional connectivity and cognition and is potentially affected by dopamine-related genes. *PLoS One* 7:e43901. doi: 10.1371/journal.pone.0043901

Rapp, A. M., Mutschler, D. E., and Erb, M. (2012). Where in the brain is nonliteral language? A coordinate-based meta-analysis of functional magnetic resonance imaging studies. *Neuroimage* 63, 600–610. doi: 10.1016/j.neuroimage.2012.06.022

Robertson, D. A., Gernsbacher, M. A., Guidotti, S. J., Robertson, R. R. W., Irwin, W., Mock, B. J., et al. (2000). Functional neuroanatomy of the cognitive process of mapping during discourse comprehension. *Psychol. Sci.* 11, 255–260. doi: 10.1111/1467-9280.00251

Sacco, K., Angeleri, R., Bosco, F. M., Colle, L., Mate, D., and Bara, B. G. (2008). Assessment battery for communication-ABaCo: a new instrument for the evaluation of pragmatic abilities. *J. Cogn. Sci.* 9, 111–157. doi: 10.17791/jcs.2008.9.2.111

Sacco, K., Angeleri, R., Colle, L., Gabbatore, I., Bara, B. G., and Bosco, F. M. (2013). ABaCo: assessment battery for communication. *Boll. Psicol. Appl.* 268, 55–58.

Sacco, K., Cauda, F., D'Agata, F., Duca, S., Zettin, M., Virgilio, R., et al. (2011). A combined robotic and cognitive training for locomotor rehabilitation: evidences of cerebral functional reorganization in two chronic traumatic brain injured patients. *Front. Hum. Neurosci.* 5:146. doi: 10.3389/fnhum.2011.00146

Sacco, K., Cauda, F., D'Agata, F., Mate, D., Duca, S., and Geminiani, G. (2009). Reorganization and enhanced functional connectivity of motor areas in repetitive ankle movements after training in locomotor attention. *Brain Res.* 1297, 124–134. doi: 10.1016/j.brainres.2009.08.049

Sacco, K., De Gaudenzi, L., and Pia, L. (2015). "Executive coaching meets cognitive neuroscience: a resting state fMRI study," in *5th Scientific Meeting of the ESN and 12th Nordic Meeting in Neuropsychology*, Tampere, University of Tampere.

Silasi, G., and Murphy, T. H. (2014). Stroke and the connectome: how connectivity guides therapeutic intervention. *Neuron* 83, 1354–1368. doi: 10.1016/j.neuron.2014.08.052

Starkstein, S. E., Federoff, J. P., Price, T. R., Leiguarda, R. C., and Robinson, R. G. (1994). Neuropsychological and neuroradiologic correlates of emotional prosody comprehension. *Neurology* 44, 515–522. doi: 10.1212/wnl.44.3_part_1.515

Strangman, G., O'Neil-Pirozzi, T. M., Burke, D., Cristina, D., Goldstein, R., Rauch, S. L., et al. (2005). Functional neuroimaging and cognitive rehabilitation for people with traumatic brain injury. *Am. J. Phys. Med. Rehabil.* 84, 62–75. doi: 10.1097/01.phm.0000150787.26860.12

Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., and Koeppe, R. A. (1998). The effect of emotional content on visual recognition memory: a PET activation study. *Neuroimage* 8, 188–197. doi: 10.1006/nimg.1998.0356

Togher, L., Wiseman-Hakes, C., Douglas, J., Stergiou-Kita, M., Ponsford, J., Teasell, R., et al. (2014). INCOG recommendations for management of cognition following traumatic brain injury, part IV: cognitive communication. *J. Head Trauma Rehabil.* 29, 353–368. doi: 10.1097/HTR.0000000000000071

Torta, D., and Cauda, F. (2011). Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. *Neuroimage* 56, 2157–2172. doi: 10.1016/j.neuroimage.2011.03.066

Wang, A. T., Lee, S. S., Sigman, M., and Dapretto, M. (2006). Developmental changes in the neural basis of interpreting communicative intent. *Soc. Cogn. Affect. Neurosci.* 1, 107–121. doi: 10.1093/scan/nsl018

Yin, S., Zhu, X., Li, R., Niu, Y., Wang, B., Zheng, Z., et al. (2014). Intervention-induced enhancement in intrinsic brain activity in healthy older adults. *Sci. Rep.* 4:7309. doi: 10.1038/srep07309

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Sui, M. Q., Liang, M., et al. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.* 29, 83–91. doi: 10.1016/j.braindev.2006.07.002

Zhou, Y., Lui, Y. W., Zuo, X. N., Milham, M. P., Reaume, J., Grossman, R. I., et al. (2014). Characterization of thalamo-cortical association using amplitude and connectivity of functional MRI in mild traumatic brain injury. *J. Magn. Reson. Imaging* 39, 1558–1568. doi: 10.1002/jmri.24310

Zou, Q., Ross, T. J., Gu, H., Geng, X., Zuo, X. N., Hong, L. E., et al. (2013). Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Hum. Brain Mapp.* 34, 3204–3215. doi: 10.1002/hbm.22136

Zou, Q. H., Zhu, C. Z., Yang, Y., Zuo, X. N., Long, X. Y., Cao, Q. J., et al. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J. Neurosci. Methods* 172, 137–141. doi: 10.1016/j.jneumeth.2008.04.012

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers
in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 06 March 2015
doi: 10.3389/fnbeh.2015.00056

Exercise-mode-related changes in task-switching performance in the elderly

*Chia-Liang Tsai * and Wen-Liang Wang*

Lab of Cognitive Neurophysiology, Institute of Physical Education, Health and Leisure Studies, National Cheng Kung University, Tainan, Taiwan

The objective of the current study was to explore the relationships between exercise modes and executive functions in the elderly. Twenty-one elderly individuals in the open-skill group, 22 in the closed-skill group, and 21 in the sedentary-behavior (control) group were recruited in the current study, and performed a task-switching paradigm during which the switches occurred unpredictably and infrequently, while the behavioral and electrophysiological performances were assessed simultaneously. The results indicated that although there were no group differences in accuracy rates, the two exercise groups exhibited shorter reaction times (RTs), and larger P2 and P3 amplitudes across all conditions compared to the control group. In addition, the exercise-mode differences revealed a relatively smaller specific cost, and faster motor RTs and larger P3 amplitudes, in the switch condition for the open-skill group in comparison with the closed-skill and control groups. These findings suggest that regularly participating in physical exercise can enhance behavioral and electrophysiological performance with regard to executive control in the elderly, and provide further evidence for the beneficial effects of open-skill exercise on the task-switching paradigm.

Keywords: open-skill, closed-skill, cognition, aging, exercise mode, task-switch

OPEN ACCESS

Edited by:
Benedetto Sacchetti, University of Turin, Italy

Reviewed by:
Federico D'Agata, University of Turin, Italy
Marco Cambiaghi, University of Turin, Italy
Corrado Bucherelli, University of Florence, Italy

****Correspondence:***
Chia-Liang Tsai, Lab of Cognitive Neurophysiology, Institute of Physical Education, Health and Leisure Studies, National Cheng Kung University, No. 1, University Road, Tainan 701, Taiwan
andytsai@mail.ncku.edu.tw

Received: *25 December 2014*
Accepted: *17 February 2015*
Published: *06 March 2015*

Citation:
Tsai C-L and Wang W-L (2015) Exercise-mode-related changes in task-switching performance in the elderly. Front. Behav. Neurosci. 9:56. doi: 10.3389/fnbeh.2015.00056

Introduction

Human life spans are increasing due to medical and technological advances. However, due to age-related declines in the volume of cerebral white matter (Sexton et al., 2014), as well as decreases in the concentration, synthesis and number of receptor sites for neurotransmitters (Chen, 2014), a broad array of cognitive functions tend to deteriorate with age (Hedden and Gabrieli, 2004). Indeed, cognitive declines among people aged 65 or older are now a pressing health care issue in many countries. If we cannot find effective primary prevention strategies to ward off the onset or progression of cognitive declines among seniors, the rapidly increasing population of elderly people will be associated with an increase in the number of individuals suffering from mild cognitive impairment, or even dementia (Pressley et al., 2003). Fortunately, numerous large prospective cohort studies have demonstrated that habitual physical exercise could attenuate the cognitive declines that often accompany aging (Colcombe et al., 2004; Wang et al., 2014; Tsai et al., 2015).

There is a growing body of literature which finds that physical activity or exercise can have the positive effects on the brain with regard to neural functioning and cognitive performance (Cassilhas et al., 2007; Smith et al., 2013), and these can be attributed to the processes of neurogenesis, vascularization, and increased blood flow in the brain (van Praag et al., 1999; Endres et al., 2003; Pereira et al., 2007), as well as changes in the secreted levels of some biomarkers in the neurochemical system (Neeper et al., 1995; Tsai et al., 2014b,c). However, there are a broad range of physical exercise modes, and this study roughly categorized them into two main types—open- and closed-skill (Di Russo et al., 2010; Dai et al., 2013). Although both exercise modes have been reported as potentially useful with regard to enhancing neuropsychological and neurophysiological performances (Tsai, 2009; Di Russo et al., 2010; Tsai et al., 2012, 2014a; Dai et al., 2013), the findings in the rather limited research literature remain rather ambiguous (Di Russo et al., 2010; Dai et al., 2013; Wang et al., 2013a,b), and thus these issues need to be further explored.

Individuals participating in open-skill types of exercise (e.g., football, table tennis, basketball, and badminton) have to continually adapt their movements and switch strategies to fit the constantly changing environment and the various skill levels of the other players. Their skills are thus predominantly externally-paced and perceptual (Di Russo et al., 2010). In contrast, the individuals participating in closed-skill types of exercise (e.g., swimming and running) are in a stable and predictable environment, and can perform the exercise according to their own pace. Therefore, their skills tend to be habitual and self-paced (Di Russo et al., 2010). For these reasons, participation in open- and closed-skill exercise requires different sets of motor skills (e.g., initiating appropriate actions, inhibiting inappropriate actions, and switching from an intended movement to another one which is a more suitable response to the opponent's actions) and different cognitive and executive process loads (e.g., such as planning, selecting relevant sensory information, obeying rules, and cognitive flexibility) (Di Russo et al., 2010). The fact that elderly people with higher levels of cardiorespiratory fitness and physical activity show better cognitive performance is well documented in the vast majority of related research (Hillman et al., 2006; Themanson et al., 2006; Netz et al., 2011; Frederiksen et al., 2014), and, compared to other aspects of cognitive functioning, executive functions are more strongly affected by exercise or physical activity (Etnier et al., 1997; Colcombe and Kramer, 2003). However, no data are available with regard to the effects of different exercise modes on executive control in the elderly with similar cardiorespiratory fitness levels and participating in open- or closed-skill exercise. The main purpose of this study was thus to explore the relationship between exercise type and executive function in the elderly.

The task-switch paradigm involves stimulus perception and identification, task-set updating, attentional reallocation, and response conflict detection and monitoring processing (Friedman et al., 2008). This cognitive task was thus adopted in the current study, since such executive functioning is required and relevant to the changing environment of the open-skill exercise. In general, the task-switch paradigm has been demonstrated to evoke the different visual response components with regard to the resulting event-related potentials (ERP), such as P2 to the target for a unique component of the switch cost or cognitive control on task-set activation (Cepeda et al., 2001; Kieffaber and Hetrick, 2005; Periáñez and Barceló, 2009), and P3 for the collection of processes subsumed under the construct of the task-set reconfiguration (Kieffaber and Hetrick, 2005; Nicholson et al., 2005). There have been previous reports of age- and physical-activity-related effects in these two ERP components in the task-switching paradigm among the elderly (Hillman et al., 2006; Friedman et al., 2008; Adrover-Roig and Barceló, 2010). Therefore, these two ERP components were used in the current study to better understand the effects of different exercise modes on electrophysiological performance in the elderly.

Recently, although Dai et al. (2013) attempted to explore the effects of different exercise modes on executive function using a task-switching paradigm with predictable and frequent switches in elderly subjects who regularly participated in either open- (e.g., table tennis or tennis) or closed-skill (e.g., jogging or swimming) exercise in the previous 3 months, they found that similar exercise effects were observed in the P3 amplitude and P3 latency, and in the reaction times (RTs) of both the global and local switch costs, between the open- and closed-skill groups. The results could be attributed to simple and well-established psychological mechanisms elicited by such a task-switching paradigm with repetition priming, during which participants could prepare the new task set in advance, which resulted in reducing the top-down, reconfiguration process (Friedman et al., 2008). van Asselen and Ridderinkhof (2000) observed age-related increases in specific switch costs when switches are infrequent (20% occurrence) and unpredictable. We thus used a cognitive task during which the switches occurred unpredictably and infrequently, and cues signaling a switch were presented at the same time as the target digits, as this is presumed to require more cognitive processing load. Since switches are unpredictable and/or occur infrequently in the open-skilled exercise situation, and the elderly subjects participating in such an exercise mode should have an advantage over those in the closed-skill one in the task-switching paradigm, we hypothesized that the subjects with long-term experience (i.e., at least 2 years) of open-skill exercise would show better switch-related neuropsychological and electrophysiological performances than those with only closed-skill experience.

Methods

Participants

Sixty-four older adults aged between 60–77 years participated in this study: 21 (seven females) in the open-skill group, 22 (eight females) in the closed-skill group, and 21 (eight females) in the sedentary-behavior (control) group. Participants in the open- and closed-skill groups separately participated in either open- (e.g., badminton or table tennis) or closed-skill exercises (e.g., jogging or swimming) at least three times per week for 30 min per session in the previous 24 months. Their demographic characteristics are presented in **Table 1**. All participants reported being free of a history of brain injury, cardiovascular or metabolic disease, neurological disorders, any medications that influence central nervous system functioning,

TABLE 1 | Demographic characteristics of the open-skill, closed-skill, and sedentary-behavior (control) groups.

	Open-skill (*n* = 21)	Closed-skill (*n* = 22)	Control (*n* = 21)	*p*
Age (years)	65.35 ± 4.21	66.03 ± 4.07	63.94 ± 3.36	0.211
Gender (female)	7	8	8	0.949
Height (cm)	164.32 ± 7.11	163.87 ± 7.50	163.94 ± 7.71	0.977
Weight (kg)	64.13 ± 10.48	62.75 ± 7.99	64.21 ± 8.98	0.841
Body Mass Index (kg/m^2)	23.68 ± 3.16	23.40 ± 2.82	23.85 ± 2.75	0.874
Education (years)	13.71 ± 2.95	13.45 ± 3.49	12.86 ± 2.03	0.619
Systolic pressure (mmHg)	122.43 ± 23.35	126.95 ± 15.85	122.29 ± 26.45	0.736
Diastolic pressure (mmHg)	76.62 ± 12.19	80.64 ± 13.58	77.29 ± 11.76	0.533
Hypertension (male)	3	4	3	0.921
Hypertension (female)	2	1	0	0.350
MMSE	27.76 ± 1.30	28.23 ± 1.11	27.29 ± 1.52	0.072
BDI-II	3.29 ± 3.35	2.95 ± 3.27	5.00 ± 3.82	0.130
Social participation	9.33 ± 2.56	10.23 ± 1.97	10.76 ± 2.45	0.143
VO_{2max} (mL/kg/min)	30.67 ± 6.56	32.81 ± 4.90	25.36 ± 4.66	< 0.001*
Memory depth	21.10 ± 4.19	21.55 ± 2.46	21.81 ± 2.99	0.777

*MMSE: mini mental state examination; BDI-II: Beck Depression Inventory, 2nd edition; *: Post hoc analyses indicated that both values of VO_{2max} are significantly higher in the open- and closed-skill groups than the control group (open-skill vs. control: p = 0.010; closed-skill vs. control: p < 0.001).*

and had normal (or corrected to normal) vision based on the minimal 20/20 standard. None of the participants showed any symptoms of psychiatric illnesses, such as depressive symptoms (all scored below 13 on the Beck Depression Inventory, 2nd edition (BDI-II, Beck et al., 1996)), dementia, or mild cognitive impairment (all scored above 26 on the Mini-Mental State Examination (MMSE, Folstein et al., 1975)). Written informed consent, as approved by the Institutional Ethics Committee of National Cheng Kung University, was provided by all the subjects, who were paid NT $1500 for their participation.

Experimental Procedure

The participants were required to make two visits to the cognitive neurophysiology laboratory. On the first visit the research assistant explained the experimental procedure, and asked the participants to complete a medical history and demographic questionnaire, MMSE, DBI II, a handedness inventory (Chapman and Chapman, 1987), social participation questionnaire (Wu, 2011), and an informed consent form. VO_{2max} was estimated by the Rockport Fitness Walking Test (Kline et al., 1987), in which the participants were required to walk one mile as quickly as possible, during which their heart rate (HR) was continuously recorded using a Polar HR monitor (RX800CX, Finland). Working memory was estimated by the digit span component of the Wechsler-IV Adult intelligence test (Wechsler, 2008). All of the participants' heights and weights were also measured to calculate their body mass indexes (BMI).

On the second visit in the same week the experimenter explained the experimental procedure after the participants arrived at the laboratory. The experiment was carried out in an acoustically shielded room with dimmed lights. Initially, the electrocap and electro-oculographic (EOG) electrodes were attached to the subjects' heads and faces before the test. Each participant was then asked to sit comfortably in front of a 17″ computer monitor, the display of which was driven by an IBM compatible personal computer with a stimulation system (Neuroscan Ltd., EI Paso, TX, USA). The distance between the computer screen and the participant was 75 cm. The task switching paradigm employed in the current study was adapted from one previously used by Friedman et al. (2008) with older adults. The stimulus was a white digit (1–9, excluding 5) presented focally in the center of the screen on a black background. The same digit was never repeated in successive trials and all of the digits were grouped into eight task blocks (blocks 1–2 and 7–8: homogeneous tasks; blocks 3–6: heterogeneous tasks), with a brief rest period in the middle of each block. The homogenous (i.e., non-switch) blocks were composed of 56 trials each. Within the homogenous block, participants only responded if the digit was more or less than 5 (e.g., blocks 1 and 7), or if the digit was odd or even (e.g., blocks 2 and 8). The heterogeneous (i.e., task-switches) blocks were composed of 112 trials, each with 10 switches. Within the heterogeneous block, participants began with one task (e.g., even/odd) and then had to switch to the other (e.g., more/less than 5), which was signaled by a simultaneously presented rectangle drawn around the digit, after a minimum of seven or a maximum of 13 intervening trials (See **Figure 1**). Participants had to press one of two buttons on a small response box held in both hands as quickly and accurately as possible. The digit was presented on the screen until the participants pressed the response button. The next trial began 500 ms following the RT response. The prompts "more less" or "even odd" appeared simultaneously with and below the digit for all trials, depending upon the side of response that was appropriate to the task. The response hand and homogenous/heterogeneous blocks were counterbalanced across participants. Participants were given the task instructions, and single-task as well as task-switch trials were practiced before the formal test until the participants understood the whole experimental procedure.

Electrophysiological Recording and Analysis

Electroencephalographic (EEG) activity was recorded from 18 scalp sites (F7, F8, F3, F4, Fz, T3, T4, C3, C4, Cz, T5, T6,

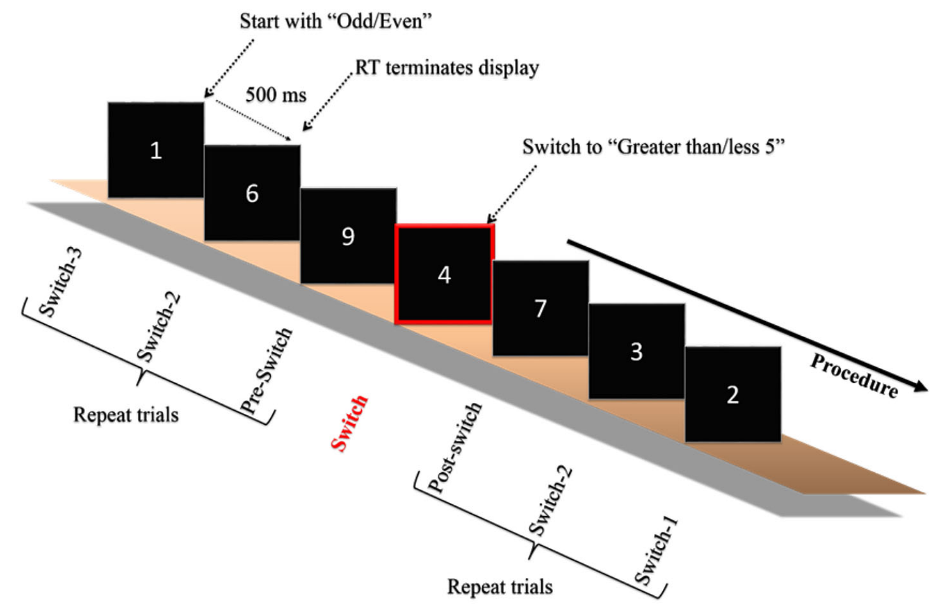


FIGURE 1 | Schematic of the experimental paradigm. Only one example of the switch blocks is depicted. Participants began with one of the two tasks (odd/even or greater/less than 5) and were required to switch when a rectangle surrounded the digit. The digit remained on the screen until the participant responded, which initiated a 500 ms interval, after which the next digit was presented. The paradigm was adapted from Friedman et al. (2008).

P3, P4, Pz, O1, O2, and Oz), using an elastic electrode cap (Quik-Cap, Compumedics Neuroscan, Inc., El Paso, TX, USA) designed for the International 10–20 System for scalp placement. Horizontal and vertical EOG activity for eye movements was monitored bipolarly with ocular electrodes placed on the supero-lateral right canthus and infero-lateral to the left eye. Scalp locations were referred to linked mastoid electrodes, while a ground electrode was placed on the mid-forehead on the Quik-Cap. Interelectrode impedance was below 5 kΩ. EEG and EOG signals were recorded with an A/D rate of 500 Hz/channel, a band-pass filter of 0.1–50 Hz, and a 60 Hz notch filter. These data were continuously written to hard disk for off-line analysis using SCAN4.3 analysis software (Compumedics Neuroscan, Inc., El Paso, TX, USA).

ERP analysis epochs extracted off-line consisted of segments from −200 ms of pre-stimulus activity to 800 ms of post-stimulus activity. ERP averages were computed for each of the digits during the switch blocks. Trials with a response error or EEG artifacts (e.g., VEOG, HEOG, and electromyogram) exceeding peak-to-peak deflections over 100 μV were rejected before averaging.

Since the effects of task switching on the P2 and P3 components in the elderly were clearly visible in frontal-central regions of the scalp in the current study (see also Kieffaber and Hetrick, 2005; Friedman et al., 2008), six electrodes (F3, Fz, F4, C3, Cz, C4) were analyzed in the current work. Two types of ERP variables (i.e., amplitudes and latencies) were measured. P2 and P3 mean amplitudes were calculated for 150--250 ms and 350–600 ms time intervals, respectively. Latencies were measured within the latency window for every participant, determined using the group grand average waveforms, and the results were equivalent for ERP elicited by all conditions and participants.

Data Processing and Statistical Analysis

Four conditions were subjected to the behavioral and ERP statistical analyses: one (i.e., non-switch trial) during homogeneous task blocks, and three (i.e., pre-switch, switch, and post-switch trials) from switch blocks according to the digit position relative to the switch trial (Friedman et al., 2008). Only the behavioral and ERP data corresponding to correct responses were analyzed. Three types of switch cost were determined by the RTs performance: (1) general-switch cost was determined by subtracting the mean RT between non-switch trials during homogeneous blocks and pre-switch trials during heterogeneous blocks; (2) specific-switch cost was determined by subtracting the mean RT between pre-switch trials and switch trials during heterogeneous blocks; and (3) post-switch cost was determined by subtracting the mean RT between pre-switch trials and post-switch trials during heterogeneous blocks.

The results for the separate behavioral performance (e.g., accuracy rate and RTs) and ERP components (i.e., P2 and P3 latencies and amplitudes) were analyzed using a mixed design, factorial, and repeated-measures analysis of variance (ANOVA). With regard to the behavioral performance of the task switching paradigm, *Group* (open-skill vs. closed-skill vs. control) was the between-subjects factor, and *Condition* (pre-switch, switch, post-switch, and non-switch trial types) was the within-subject factor, with the accuracy rates and mean RTs of accepted trials serving as the dependent variables. For the ERP P2 and P3 measures, *Group* (open-skill vs. closed-skill vs. control) was also the between-subjects factor, and *Condition* (pre-switch, switch, post-switch, and non-switch trial types) and *Electrode* (F3, Fz, F4, C3, Cz, C4) were the within-subjects variables. Where a significant difference occurred, Bonferroni *post hoc* analyses were performed. Significant alpha levels were adjusted with the Greenhouse-Geisser (G-G) epsilon correction whenever a major violation of the sphericity assumption was detected in repeated measures ANOVA, with more than two degrees of freedom (Vasey and Thayer, 1987). The effect size (i.e., partial η^2: η_p^2) is also reported to complement the use of significance testing, with the following conventions adopted to determine the magnitude of the mean effect size: <0.08 (small effect size), between 0.08 to 0.14 (medium effect size), and >0.14 (large effect size). Since the correction factor reduces the degrees of freedom of the usual *F*-test, and often results in non-integer values, only the corrected probability values and degrees of freedom are reported. In addition, since the neural processes responsible for switch costs are elicited at the time of target presentation (Kieffaber and Hetrick, 2005), sensitivity indices (general-, specific, and post-switch cost for P2 and P3 latency and amplitude) were also calculated, and the mean amplitudes and latencies of P2 and P3 were submitted to a series of Pearson product-moment correlation analyses with the mean RT switch costs (i.e., general-, specific-, and post-switch costs), respectively. A value of $p < 0.05$ was considered to be significant.

Results

As shown in **Table 1**, the three (i.e., open-skill, closed-skill, and control) groups were matched at the group level on age, height, weight, BMI, systolic and diastolic pressure (all *p*s > 0.05). The levels of education, cognitive impairment, social participation, depression, and memory depth (all *p*s > 0.05) also revealed non-significant differences across the three groups. Only the cardiorespiratory fitness showed significant differences among the three groups ($F_{(2,61)} = 10.63$, $p < 0.001$). *Post hoc* comparisons demonstrated that the open- and closed-skill groups had significantly larger maximal oxygen uptake (VO_{2max}) than the control group (open-skill vs. control: $p = 0.001$; close-skill vs. control: $p < 0.001$), and the level of cardiorespiratory fitness was matched between the open- and closed-skill groups ($p = 0.441$).

Behavioral Performance

As seen in **Figure 2**, the results of repeated-measures ANOVA on the mean accuracy rate revealed a significant main effect of *Condition* ($F_{(3,183)} = 9.06$, $p < 0.001$, $\eta_p^2 = 0.13$), indicating that a higher percentage of errors were found in the switch (88.0%) and post-switch (87.7%) conditions relative to pre-switch (91.3%) and non-switch (90.8%) ones. Neither significant main effects of *Group* ($F_{(2,61)} = 0.04$, $p = 0.957$) nor significant interactions between *Group* and *Condition* ($F_{(6,183)} = 2.07$, $p = 0.093$) were obtained.

The repeated-measures ANOVA on the grand mean RT data revealed a significant main effect of *Group* ($F_{(2,61)} = 3.35$, $p = 0.042$, $\eta_p^2 = 0.10$), indicating that the control group (1261.73 ms) showed overall slowing relative to the two exercise groups (open-skill: 1116.21 ms; closed-skill: 1141.6 ms) across the four conditions. The main effect of *Condition* ($F_{(3,183)} = 1861.58$, $p < 0.001$, $\eta_p^2 = 0.97$) was also significant, with the following gradient: switch (1759.4 ms) > post-switch (1229.64 ms) > pre-switch (855.65 ms) > non-switch (847.68 ms). These main effects were superseded by the *Time* × *Condition* ($F_{(6,183)} = 4.62$, $p = 0.001$, $\eta_p^2 = 0.13$) interactions. *Post hoc* analyses indicated that the open-skill group responded faster in the switch condition than the closed-skill or control groups.

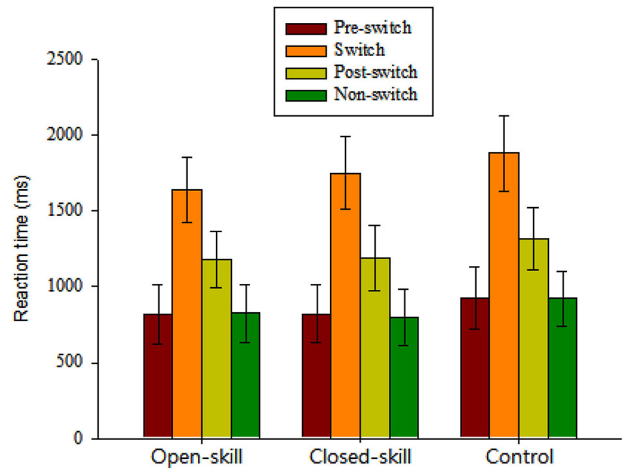


FIGURE 2 | Grand mean RT data (mean ± SD) for pre-switch, switch, and post-switch trials during the heterogeneous blocks and non-switch trials during homogeneous blocks in the open-skill, closed-skill, and control groups (Note: The control group showed overall slowing relative to the two exercise groups across the four conditions; the open-skill group responded faster in the switch condition than the close-skill or control groups).

In terms of RT switch costs, one-way ANOVA showed only a significant main effect of *Group* ($F_{(2,61)} = 7.30$, $p = 0.001$) for the specific-switch cost. *Post hoc* analyses indicated a smaller specific-switch cost in the open-skill group (820.52 ± 112.54 ms) than in the closed-skill (940.30 ± 144.3 ms) or control groups (959.35 ± 124.51 ms).

Electrophysiological Performance

Figure 3 shows the grand-average ERP waveforms obtained from the six electrodes in the three groups. The topography scalp distribution maps of the stimulus-elicited positivities, P2 and P3 event-related potential components, for four conditions in the three groups are illustrated in **Figure 4**.

P2 Latency

As seen in **Figure 3**, there was only a significant effect of *Electrode* ($F_{(5,305)} = 4.68$, $p = 0.002$, $\eta_p^2 = 0.07$) on the P2 latency, with the following gradient: Cz (190.42 ms) > C4 (187.62 ms) > C3 (187.34 ms) > F4 (184.39 ms) > Fz (183.64 ms) > F3 (183.51 ms). No significant difference was observed between the three groups in the P2 latency, without any other main effect or interaction.

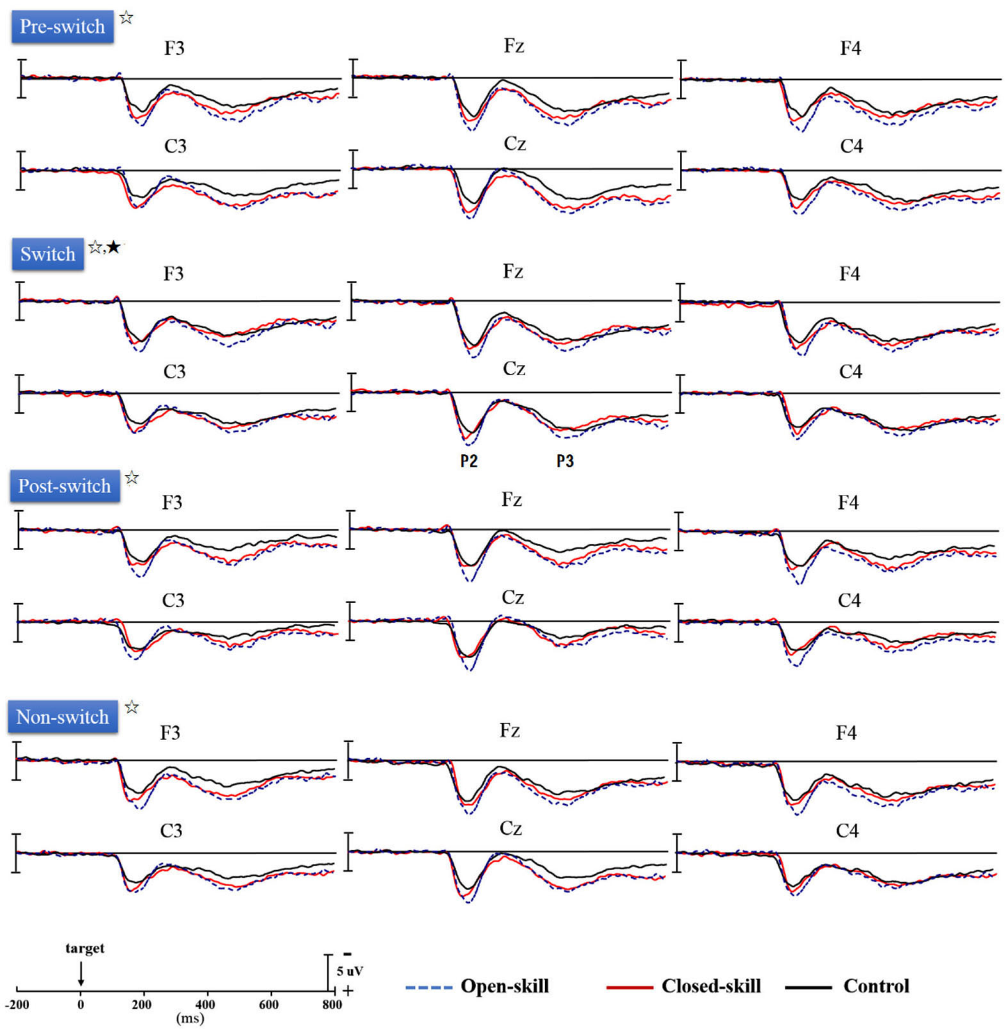


FIGURE 3 | Grand-average ERPs for four conditions (pre-switch, switch, post-switch, non-switch) at six electrodes (F3, Fz, F4, C3, Cz, C4) in the open-skill, closed-skill, and control groups (☆: open- and closed-skill groups showed significantly larger P2 and P3 amplitudes than the control group.; ★: The open-skill group had a significantly larger P3 amplitude than the closed-skill and control groups).

P2 Amplitude

As seen from **Figure 3**, *Group* had significant effects ($F_{(2,61)}$ = 12.88, $p < 0.001$, $\eta_p^2 = 0.30$) on the P2 amplitude, indicating that the open-skill (10.42 ± 2.10 μV) and closed-skill (8.44 ± 2.25 μV) groups showed significantly larger P2 amplitudes than the control (6.92 ± 2.38 μV) group (open-skill vs. control, $p < 0.001$; closed-skill vs. control, $p = 0.016$) across all conditions. There were significant effects of *Condition* ($F_{(3,183)}$ = 5.96, $p = 0.001$, $\eta_p^2 = 0.09$) and *Electrode* ($F_{(5,305)}$ = 45.32, $p < 0.001$, $\eta_p^2 = 0.43$) on the P2 amplitude, with the following gradient: switch (9.21 μV) > non-switch (8.78 μV) > pre-switch (8.49 μV) > post-switch (7.91 μV) in the four conditions, and Fz (9.55 μV) > Cz (9.27 μV) > F4 (8.94 μV) > F3 (8.51 μV) > C4 (8.05 μV) > C3 (7.23 μV). The effects of the interactions of *Group* × *Electrode* ($F_{(10,305)}$ = 3.25, $p = 0.001$, $\eta_p^2 = 0.10$), *Condition* × *Electrode* ($F_{(15,915)}$ = 3.52, $p < 0.001$, $\eta_p^2 = 0.06$), and *Group* × *Condition* × *Electrode* ($F_{(30,915)}$ = 1.86, $p = 0.004$, $\eta_p^2 = 0.06$) on P2 amplitudes were also significant. However, the effect of the interaction of *Group* × *Condition* was not significant.

P3 Latency

No significant difference was observed between the three groups in the P3 latency, without any other main effect or interaction (see **Figure 3**).

P3 Amplitude

As shown in **Figure 3**, *Group* had significant effects ($F_{(2,61)}$ = 8.21, $p = 0.001$, $\eta_p^2 = 0.21$) on the P3 amplitude, indicating that the open-skill (7.77 ± 2.09 μV) and closed-skill (6.72 ± 2.24 μV) groups showed significantly larger P3 amplitudes than the control (5.00 ± 2.40 μV) group (open-skill vs. control, $p = 0.001$; closed-skill vs. control, $p = 0.043$) across all conditions. There

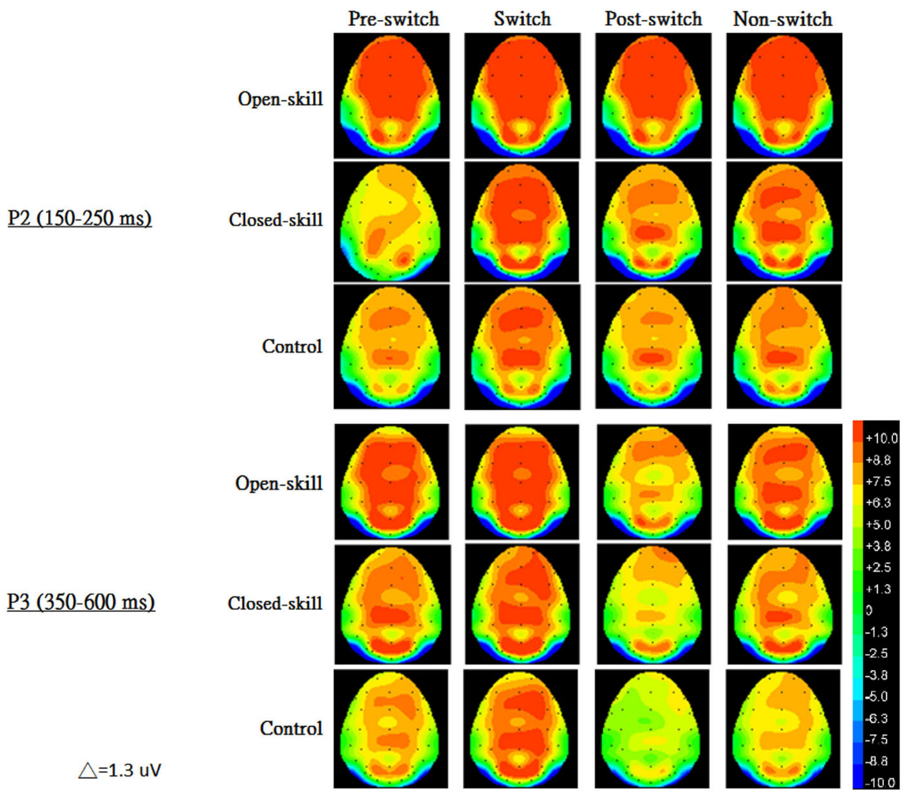


FIGURE 4 | The topography scalp distribution maps of the stimulus-elicited positivities, P2 and P3 event-related potential components, for four conditions (pre-switch, switch, post-switch, non-switch) in the open-skill, closed-skill, and control groups.

were significant effects of *Condition* ($F_{(3,183)} = 19.66$, $p < 0.001$, $\eta_p^2 = 0.24$) and *Electrode* ($F_{(5,305)} = 19.27$, $p < 0.001$, $\eta_p^2 = 0.24$) on the P3 amplitude, with the following gradient: pre-switch (7.28 μV) > switch (7.16 μV) > non-switch (6.40 μV) > post-switch (5.13 μV) in the four conditions, and F4 (7.30 μV) > Fz (6.96 μV) > Cz (6.60 μV) > F3 (6.18 μV) > C3 (6.05 μV) > C4 (5.87 μV). The effects of the interactions of *Group* × *Condition* ($F_{(6,183)} = 2.37$, $p = 0.031$, $\eta_p^2 = 0.07$), *Group* × *Electrode* ($F_{(10,305)} = 3.01$, $p = 0.001$, $\eta_p^2 = 0.09$), and *Condition* × *Electrode* ($F_{(15,915)} = 6.25$, $p < 0.001$, $\eta_p^2 = 0.09$) on P3 amplitudes were also significant. In terms of the significant effect of *Group* × *Condition*, *post hoc* analyses revealed that, compared to the control group, the P3 amplitudes were significantly larger in the two exercise groups in the pre-switch, post-switch, and non-switch conditions; and the open-skill group (8.69 ± 2.99 μV) had a significantly larger P3 amplitude than the closed-skill (6.44 ± 2.78 μV) and control groups (6.35 ± 3.00 μV) (open-skill vs. closed-skill: $p = 0.043$; open-skill vs. control: $p = 0.035$) only in the switch condition.

Correlation Analysis

Neither P2 nor P3 performance showed any pattern of significant correlations with behavioral responses in the general-, specific-, and post-switch costs in the three groups, respectively.

Discussion

The purpose of this study was to explore the exercise-mode-related changes in task-switching performance in the elderly. The results of study confirm that, relative to the control group, the two exercise groups exhibited shorter RTs and larger P2 and P3 amplitudes across all conditions. In addition, the elderly subjects participating in the open-skill exercise showed smaller specific costs, and faster motor RTs and larger P3 amplitudes in the switch condition when compared to the closed-skill or control groups when performing the task-switching paradigm.

With regard to behavioral performance, the RT results on the four conditions indicate that the four trial types required increasing amounts of executive processing when the participants performed the task switching paradigm, consistent with a previous study (Friedman et al., 2008). That is, relative to the pre-switch trials, switch and post-switch trials engendered considerable prolongation of RTs, which produced specific switch and post-switch costs, respectively. The difference in RTs among the three groups was present across the four conditions of the task-switch paradigm, in which the control group showed significantly slower response times when compared to both the open- and closed-skill groups, suggesting that the elderly subjects who regularly participated in physical exercise displayed a generalized reduction in the time efficiency of the central processing of cognitive functions in comparison to the sedentary-behavior group. This is compatible with the findings in Hillman et al. (2006) and Dai et al. (2013) that elderly people with higher levels of physical activity or regular participation in open- or closed-skill exercise showed shorter RTs than those with less physical activity or irregular exercise. However, no differences in accuracy rates among the three groups were found in this study, and this supports the view that the RT differences across all conditions could be attributed to the differences in processing time between the control group and the two exercise groups, demonstrating that the generalized reduction in the time efficiency of the central processing of cognitive functions could be regarded as a general advantage of regular participation in sports and other forms of exercise over a sedentary lifestyle (Di Russo et al., 2010; Tsai et al., 2014a, 2015).

On the other hand, the open-skill group showed faster RTs in the switch condition than the closed-skill or control groups. Given that participating in the open-skill exercise modes could facilitate differential advanced preparation for an upcoming switch (Di Russo et al., 2010), these findings indicate that the elderly people engaging such an exercise mode could become better at switching from one task to another, as this constantly happens in an open-skill exercise environment. The open-skill group also had a lower specific-switch cost than the closed-skill and control groups, in contrast to the results in Dai et al. (2013), which reported that the facilitative effect of open-skill exercise was not observed in local switch costs (i.e., the RT differences between the switch and non-switch trials in the heterogeneous condition). There are several plausible mechanisms for the contrasting results. First, the switch predictability in switch-related processing was different in the task-switching paradigms used in the current and earlier works. Dai et al. (2013) adopted a series of pair-trials (e.g., AABBAABB) in their cognitive task, which made a greater demand on working memory, because the participants needed to remember where they were in the sequence. In the current study, one task (e.g., even/odd) switches to the other (e.g., more/less than 5) after a long repetition of sequences (i.e., a minimum of seven or a maximum of 13 intervening trials), and this design could produce a great deal of interference from the prior task set on the switch trial. Moreover, the infrequent occurrence of switch trials (less than 10%) in the present study meant that it was difficult for the participants to predict when a switch would occur, and thus they were likely to adopt a strategy of keeping the current task set in their working memory, and reconfigured this to suit a new task set only when a change in task was signaled by the cue (Monsell and Mizon, 2006; Friedman et al., 2008). Further, given the lack of a cue-and-target preparatory interval in the task-switching paradigm in the present study, the participants did not have enough time to reallocate attention to the new task set according to the cue preceding the target, nor update the procedural rules by retrieving them from memory. Since open-skill exercise could favor response flexibility and foster greater stability of motor responses, and the open-skill exercise environment is unpredictable and always changing (Di Russo et al., 2010), the elderly subjects who regularly participated in such an exercise mode could see greater cognitive flexibility when switching from pre-switch to switch trials during the heterogeneous conditions, as designed in the current study.

In addition, no difference in the general-switch cost was found in the current study, suggesting that the process of selecting between and coordinating the two competing tasks appeared to be comparable among the three groups (Friedman et al., 2008). However, the facilitative effect of open-skill exercise in the elderly was observed with regard to the global switch cost (i.e., the RT differences between the homogeneous and heterogeneous conditions) in a previous study (Dai et al., 2013). As noted earlier, these discrepancies may result from procedural differences in the task-switching paradigm. Since Dai et al. (2013) adopted an alternating runs paradigm with a lack of switch cues, the participants had to keep track of which task rules were operative and the sequence of the trials, which would produce higher working memory loads. In contrast, when the participants performed the task-switching paradigm in the current study, a cue carried task-relevant information to remind them of the response key assignments on each trial. Accordingly, the lower working memory demands could, at least in part, have led to the similar general-switch costs found in the present study (Friedman et al., 2008).

Event-related potential P2 is associated with a unique component of switch cost (Kieffaber and Hetrick, 2005). In the present study, the P2 latencies were not significantly different between the three groups. However, there was a significant *Group* effect on the P2 amplitude, indicating that two exercise groups showed significantly larger P2 amplitudes across all conditions relative to the control group. Previous studies have demonstrated that the elderly need to meet more processing demands during maintenance and retrieval of two task sets concurrently held in working memory when performing a task-switching paradigm task (DiGirolamo et al., 2001; Goffaux et al., 2006). Since P2 amplitude is sensitive to task switching when a shift of target modality is involved (Kieffaber and Hetrick, 2005; Adrover-Roig and Barceló, 2010), the findings of the present study thus lend support to the hypothesis that regularly participating in the physical exercise (e.g., open- and closed-skill modes) could facilitate better cognitive control with regard to task-set activation (i.e., inhibitory control of responses for a previously performed task) among elderly subjects (Cepeda et al., 2001; Periáñez and Barceló, 2009), and/or enhanced cue-task retrieval processes (West and Travers, 2008). Although none of the earlier studies tried to explore the relationship between exercise and cognition with regard to the effects of this on the P2 components when elderly subjects performed a task-switching paradigm task, one previous study did find a positive association between physical activity and error-related negativity in elderly individuals, reflecting a greater efficiency in dealing with the conflicts arising during trials among those subjects who engaged in more physical activity (Themanson et al., 2006). It is worth pointing out that P2 component is associated with switch cost (Kieffaber and Hetrick, 2005), and thus the two exercise groups which showed larger P2 amplitudes should exhibit better performance with regard to these costs. However, only the open-skill group had smaller specific-switch costs when compared to the closed-skill and control groups. Indeed, previous studies found that the magnitude of switch costs does not depend on the amount of physical activity in the elderly (Hillman et al., 2006; Themanson et al., 2006). In addition, Themanson et al. (2006) found that sedentary elderly adults who engaged in erobic exercise (a closed-skill exercise mode) for 6 months showed a significantly greater reduction in the magnitude of the switch cost when compared to those in the strength and flexibility exercise (also a closed-skill exercise mode) group. Given the results of the current and previous studies, cardiorespiratory fitness seems to be the potential facilitative factor with regard to the P2 amplitude in the elderly. However, only the elderly who engaged in open-skill exercise and also had a higher cardiorespiratory capacity exhibited the beneficial effect on specific-switch cost. In addition, the switch sensitivities of the P2 and P3 components were not related to the RTs in the general-, specific-, and post-switch costs in the current study, indicating that the stimulus-dependent neural processes may not contribute to RT switch costs in the current task-switching paradigm, and the elderly with higher cardiorespiratory fitness via different exercise modes could see distinctive behavioral and electrophysiological effects.

The P3 latencies were not significantly different among the three groups, suggesting that all participants showed similar perceptual/central processing (Polich, 1997) when performing the task-switch paradigm task in the current study. The main *Group, Condition*, and *Group* × *Condition* effects on P3 amplitude were revealed in the present study. The P3 amplitude observed in the current study reflects task-set updating processes and attentional allocation to the stimuli in the service of updating the memory (Polich, 1997; Friedman et al., 2008). There were significant differences in the P3 amplitudes among the four conditions in the current task-switching paradigm for the elderly participants, demonstrating that the frontal-central networks responsible for task-set updating processes and attentional allocation were not compromised in the elderly subjects in the present study when performing the cognitive task. Additionally, this finding also suggests that the elderly participants' reconfiguration of response mapping specific to different conditions was intact, which could appropriately reflect the neural mechanisms at work in processing the current task-switching paradigm. In terms of between-group comparison, the two exercise groups showed larger P3 amplitudes across all conditions relative to the control group, similar to the finding in Hillman et al. (2006) of a larger P3 amplitude for the active rather than for the sedentary elderly when performing the task switching paradigm. Given the lack of preparatory interval and the lower infrequency of switches in the cognitive task, the participants must allocate their attentional resources to predict when a switch would occur and to prepare a new task set before cue occurrence. Since elderly people have been found to have difficulties in reallocating attentional resources (Friedman et al., 2001), and to suffer from age-related disturbances in the task-set updating process (West and Moore, 2005), the results of the current study indicate that regularly participating in physical exercise seems to facilitate the attentional set that makes it possible to better evaluate the stimulus in either of the two tasks.

The open-skill group showed a significantly larger P3 amplitude in the switch condition when performing the task-switching paradigm compared to the closed-skill and control groups. Since the P3 amplitude in such a condition reflects the collection of processes subsumed under the construct of the task-set reconfiguration (Karayanadis et al., 2003; Kieffaber and Hetrick, 2005; Nicholson et al., 2005), and cognitive processing plasticity can be modulated by the execution of the open-skill exercises (Fontani et al., 1999; Iwadate et al., 2005), the current study seems to demonstrate that participating in the open-skill exercise mode could enhance these cognitive processes in the elderly subjects. However, the task-set updating processes in the homogeneous task, pre-switch condition, and post-switch condition were not be affected by the different types of exercise. Additionally, the larger P3 amplitude of the open-skill group only appeared in the switch condition, implying that the enhanced P3 amplitude was selective for cognitive processing related to tasks requiring stimulus perception and identification, task-set updating, response conflict detection and monitoring processing (Friedman et al., 2008). However, this finding for P3 amplitude differed to that in a previous study (Dai et al., 2013), in which the closed-skill and open-skill groups showed similar electrophysiological performances in the P3 component (e.g., P3 amplitude and P3 latency) in the homogenous and heterogeneous blocks. The most likely explanation for the contrasting results might be the elderly subjects' exercise experience (3 months in Dai et al.'s (2013) study vs. 24 months in the current study), and the different characteristics of the task-switch paradigm, as mentioned above. Since attentional allocation and cognitive processing are more susceptible to the effects of interceptive sports (e.g., badminton and table tennis) than static ones (e.g., swimming and jogging) (Voss et al., 2010), and cognitive adaptations (e.g., strengthened synaptic neurotransmission and increased neurogenesis) are available in complex environments that engage rich cognitive loadings (van Praag et al., 2000; Artola et al., 2006; Gajewski et al., 2010), we assumed that the elderly subjects participating in the open-skill exercise for longer periods would see greater behavioral and neurobiological consequences with regard to specific switching aspects of the executive functions (van Praag et al., 2000; Dai et al., 2013).

Although we rigorously controlled some important factors which could mediate the exercise-cognition association (e.g., blood pressure, depression and social stimulation, Miller et al., 2012), there are still some potential limitations in the current study. First, the elderly subjects with higher cardiorespiratory fitness (i.e., open- and closed-skill groups) showed better behavioral and electrophysiological performances when performing a cognitive task involving executive control compared to those with lower cardiorespiratory fitness (i.e., the control group). The results conform to the trend seen in a large number of previous studies (Hillman et al., 2006; Themanson et al., 2006; Netz et al., 2011; Frederiksen et al., 2014), showing that a general reduction in cardiorespiratory fitness and lower physical activity levels may contribute to worse executive control functioning. However, when the elderly subjects with higher cardiorespiratory fitness were categorized into open- or closed-skill exercise mode groups in the present study, we found more detailed differences in the behavioral and electrophysiological performances between the two elderly groups, as mentioned above. However, previous studies demonstrated that cardiorespiratory fitness is the main factor that affects cognitive processing (Stroth et al., 2009; Tsai et al., 2014b). It remains an open question as to whether elderly subjects participating in the open-skill exercise mode and with abundant exercise experience, but without higher cardiorespiratory fitness, could still exhibit different cognitive performances on specific switch aspects of executive functions in the task-switching paradigm. Future research efforts should thus address this issue. Secondly, the present experiment was a cross-sectional study, and thus the elderly subjects participating in the open-skill exercise mode might inherently have had better executive functioning (e.g., task switching) compared to their counterparts participating in the closed-skill exercise mode, and this may have induced them to adopt this kind of exercise, and thus also show better behavioral and electrophysiological performances in the switch condition when performing the task-switching paradigm. Future studies could thus examine the contributions of different exercise-mode mechanisms responsible for the specific types of executive-control functioning via longitudinal experiments regarding specific exercise-mode interventions, in which elderly subjects without any exercise experience are randomly assigned to different exercise modes (Snowden et al., 2011).

A healthy lifestyle is well known to protect against the development of numerous medical disorders. Indeed, the elderly subjects who regularly participated in open- or closed-skill exercise exhibited better behavioral and electrophysiological performances when performing the task-switching paradigm in the current study. Additionally, given that participating in open-skill exercise stimulates specific types of executive-control functioning, open-skill exercise (e.g., table tennis or badminton) could be an effective physical activity mode that can help elderly people to better deal with two competing tasks and task-set/memory updating processing, especially in the switch condition.

Acknowledgments

This research was supported by a grant from the National Science Council in Taiwan (NSC 102-2628-H-006-003-MY3). The authors are also grateful to the participants who gave their precious time to facilitate the work reported here.

References

Adrover-Roig, D., and Barceló, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task switching. *Cortex* 46, 434–450. doi: 10.1016/j.cortex.2009.09.012

Artola, A., von Frijtag, J. C., Fermont, P. C., Gispen, W. H., Schrama, L. H., Kamal, A., et al. (2006). Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment. *Eur. J. Neurosci.* 23, 261–272. doi: 10.1111/j.1460-9568.2005.04552.x

Beck, A. T., Steer, R. A., and Brown, G. K. (1996). *BDI-II: 2nd Edition Manual*. San Antonio, TX: The Psychological Corporation.

Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., et al. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Med. Sci. Sports Exerc.* 39, 1401–1407. doi: 10.1249/mss.0b013e318060111f

Cepeda, N. J., Kramer, A. F., and Gonzalez de Sather, J. C. (2001). Changes in executive control across the life span: examination of task switching performance. *Dev. Psychol.* 37, 715–730. doi: 10.1037/0012-1649.37.5.715

Chapman, L. J., and Chapman, J. P. (1987). The measurement of handedness. *Brain Cogn.* 6, 175–183. doi: 10.1016/0278-2626(87)90118-7

Chen, J. F. (2014). Adenosine receptor control of cognition in normal and disease. *Int. Rev. Neurobiol.* 119, 257–307. doi: 10.1016/B978-0-12-801022-8.00012-X

Colcombe, S., and Kramer, A. F. (2003). Fitness effects on the cognitive function of elder adults: a meta-analytic study. *Psychol. Sci.* 14, 125–130. doi: 10.1111/1467-9280.t01-1-01430

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., et al. (2004). Cardiovascular fitness, cortical plasticity and aging. *Proc. Natl. Acad. Sci. U S A* 101, 3316–3321. doi: 10.1073/pnas.0400266101

Dai, C. T., Chang, Y. K., Huang, C. J., and Hung, T. M. (2013). Exercise mode and executive function in older adults: an ERP study of task-switching. *Brain Cogn.* 83, 153–162. doi: 10.1016/j.bandc.2013.07.007

DiGirolamo, G. J., Kramer, A. F., Barad, V., Cepeda, N. J., Weissman, D. H., Milham, M. P., et al. (2001). General and task-specific frontal lobe recruitment in older adults during executive processes: a fMRI investigation of task-switching. *Neuroreport* 12, 2065–2071. doi: 10.1097/00001756-200107030-00054

Di Russo, F., Bultrini, A., Brunelli, S., Delussu, A. S., Polidori, L., Taddei, F., et al. (2010). Benefits of sports participation for executive function in disabled athletes. *J. Neurotrauma* 27, 2309–2319. doi: 10.1089/neu.2010.1501

Endres, M., Gertz, K., Lindauer, U., Katchanov, J., Schultze, J., Schröck, H., et al. (2003). Mechanisms of stroke protection by physical activity. *Ann. Neurol.* 54, 582–590. doi: 10.1002/ana.10722

Etnier, J. L., Salazar, W., Landers, D. M., Petruzello, S. J., Han, M., and Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. *J. Sport Exerc. Psychol.* 19, 249–277.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Fontani, G., Maffei, D., Cameli, S., and Polidori, F. (1999). Reactivity and event-related potentials during attentional tests in athletes. *Eur. J. Appl. Physiol. Occup. Physiol.* 80, 308–317. doi: 10.1007/s004210050597

Frederiksen, K. S., Verdelho, A., Madureira, S., Bäzner, H., O'Brien, J. T., Fazekas, F., et al. (2014). Physical activity in the elderly is associated with improved executive function and processing speed: the LADIS study. *Int. J. Geriatr. Psychiatry* doi: 10.1002/gps.4220. [Epub ahead of print].

Friedman, D., Cycowicz, Y. M., and Gaeta, H. (2001). The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neurosci. Biobehav. Rev.* 25, 355–373. doi: 10.1016/s0149-7634(01)00019-7

Friedman, D., Nessler, D., Johnson, R. Jr., Ritter, W., and Bersick, M. (2008). Age-related changes in executive function: an event-related potential (ERP) investigation of task-switching. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 15, 95–128. doi: 10.1080/13825580701533769

Gajewski, P. D., Wild-Wall, N., Schapkin, S. A., Erdmann, U., Freude, G., and Falkenstein, M. (2010). Effects of aging and job demands on cognitive flexibility assessed by task switching. *Biol. Psychol.* 85, 187–199. doi: 10.1016/j.biopsycho.2010.06.009

Goffaux, P., Phillips, N. A., Sinai, M., and Pushkar, D. (2006). Behavioural and electrophysiological measures of task-switching during single and mixed-task conditions. *Biol. Psychol.* 72, 278–290. doi: 10.1016/j.biopsycho.2005.11.009

Hedden, T., and Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat. Rev. Neurosci.* 5, 87–96. doi: 10.1038/nrn1323

Hillman, C. H., Kramer, A. F., Belopolsky, A. V., and Smith, D. P. (2006). A cross-sectional examination of age and physical activity on performance and event-related brain potentials in a task switching paradigm. *Int. J. Psychophysiol.* 59, 30–39. doi: 10.1016/j.ijpsycho.2005.04.009

Iwadate, M., Mori, A., Ashizuka, T., Takayose, M., and Ozawe, T. (2005). Long-term physical exercise and somatosensory event-related potentials. *Exp. Brain Res.* 160, 528–532. doi: 10.1007/s00221-004-2125-5

Karayanadis, F., Coltheart, M., Michie, P. T., and Murphy, K. (2003). Electrophysiological correlates of anticipatory and poststimulus components of task switching. *Psychophysiology* 40, 329–348. doi: 10.1111/1469-8986.00037

Kieffaber, P. D., and Hetrick, W. P. (2005). Event-related potential correlates of task switching and switch costs. *Psychophysiology* 42, 56–71. doi: 10.1111/j.1469-8986.2005.00262.x

Kline, G. M., Porcari, J. P., Hintermeister, R., Freedson, P. S., Ward, A., McCarron, R. F., et al. (1987). Estimation of VO_{2max} from a one-mile track walk, gender, age and body weight. *Med. Sci. Sports Exerc.* 19, 253–259. doi: 10.1249/00005768-198706000-00012

Miller, D. I., Taler, V., Davidson, P. S., and Messier, C. (2012). Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiol. Aging* 33, 622.e29–622.e43. doi: 10.1016/j.neurobiolaging.2011.02.020

Monsell, S., and Mizon, G. A. (2006). Can the task-cuing paradigm measure an endogenous task-set reconfiguration process? *J. Exp. Psychol. Hum. Percept. Perform.* 32, 493–516. doi: 10.1037/0096-1523.32.3.493

Neeper, S. A., Gómez-Pinilla, F., Choi, J., and Cotman, C. (1995). Exercise and brain neurotrophins. *Nature* 373:109. doi: 10.1038/373109a0

Netz, Y., Dwolatzky, T., Zinker, Y., Argov, E., and Agmon, R. (2011). Aerobic fitness and multidomain cognitive function in advanced age. *Int. Psychogeriatr.* 23, 114–124. doi: 10.1017/s1041610210000797

Nicholson, R., Karayanidis, F., Poboka, D., Heathcote, A., and Michie, P. T. (2005). Electrophysiological correlates of anticipatory task-switching processes. *Psychophysiology* 42, 540–554. doi: 10.1111/j.1469-8986.2005.00350.x

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., et al. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U S A* 104, 5638–5643. doi: 10.1073/pnas.0611721104

Periáñez, J. A., and Barceló, F. (2009). Updating sensory versus task representations during task-switching: insights from cognitive brain potentials in humans. *Neuropsychologia* 47, 1160–1172. doi: 10.1016/j.neuropsychologia.2009.01.014

Polich, J. (1997). EEG and ERP assessment of normal aging. *Electroencephalogr. Clin. Neurophysiol.* 104, 244–256. doi: 10.1016/s0168-5597(97)96139-6

Pressley, J. C., Trott, C., Tang, M., Durkin, M., and Stern, Y. (2003). Dementia in community-dwelling elderly patients: a comparison of survey data, medicare claims, cognitive screening, reported symptoms and activity limitations. *J. Clin. Epidemiol.* 56, 896–905. doi: 10.1016/s0895-4356(03)00133-1

Sexton, C. E., Walhovd, K. B., Storsve, A. B., Tamnes, C. K., Westlye, L. T., Johansen-Berg, H., et al. (2014). Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. *J. Neurosci.* 34, 15425–15436. doi: 10.1523/JNEUROSCI.0203-14.2014

Smith, J. C., Nielson, K. A., Antuono, P., Lyons, J. A., Hanson, R. J., Butts, A. M., et al. (2013). Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *J. Alzheimers Dis.* 37, 197–215. doi: 10.3233/JAD-130467

Snowden, M., Steinman, L., Mochan, K., Grodstein, F., Prohaska, T. R., Thurman, D. J., et al. (2011). Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. *J. Am. Geriatr. Soc.* 59, 704–716. doi: 10.1111/j.1532-5415.2011.03323.x

Stroth, S., Kubesch, S., Dieterle, K., Ruchsow, M., Heim, R., and Kiefer, M. (2009). Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. *Brain Res.* 1269, 114–124. doi: 10.1016/j.brainres.2009.02.073

Themanson, J. R., Hillman, C. H., and Curtin, J. J. (2006). Age and physical activity influences on action monitoring during task switching. *Neurobiol. Aging* 27, 1335–1345. doi: 10.1016/j.neurobiolaging.2005.07.002

Tsai, C. L. (2009). The effectiveness of exercise intervention on inhibitory control in children with developmental coordination disorder: using a visuospatial attention paradigm as a model. *Res. Dev. Disabil.* 30, 1268–1280. doi: 10.1016/j.ridd.2009.05.001

Tsai, C. L., Chang, Y. K., Chen, F. C., Hung, T. M., Pan, C. Y., and Wang, C. H. (2014a). Effects of cardiorespiratory fitness enhancement on deficits in visuospatial working memory in children with developmental coordination disorder: a cognitive electrophysiological study. *Arch. Clin. Neuropsychol.* 29, 173–185. doi: 10.1093/arclin/act081

Tsai, C. L., Chen, F. C., Pan, C. Y., Wang, C. H., Huang, T. H., and Chen, T. C. (2014b). Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF level. *Psychoneuroendocrinology* 41, 121–131. doi: 10.1016/j.psyneuen.2013.12.014

Tsai, C. L., Wang, C. H., Pan, C. Y., Chen, F. C., and Huang, T. H. (2015). The effect of long-term resistance exercise on the relationship between neurotrophin levels and cognitive performance in the elderly. *Front. Behav. Neurosci.* 9:23. doi: 10.3389/fnbeh.2015.00023

Tsai, C. L., Wang, C. H., Pan, C. Y., Chen, F. C., Huang, T. H., and Chou, F. Y. (2014c). Executive function and endocrinological responses to acute resistance exercise. *Front. Behav. Neurosci.* 8:262. doi: 10.3389/fnbeh.2014.00262

Tsai, C. L., Wang, C. H., and Tseng, Y. T. (2012). Effects of exercise intervention on event-related potential and task performance indices of attention networks in children with developmental coordination disorder. *Brain Cogn.* 79, 12–22. doi: 10.1016/j.bandc.2012.02.004

van Asselen, M., and Ridderinkhof, K. R. (2000). Shift costs of predictable and unexpected set shifting in young and older adults. *Psychologica Beligica* 40, 259–273.

van Praag, H., Kempermann, G., and Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2, 266–270. doi: 10.1038/6368

van Praag, H., Kempermann, G., and Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 1, 191–198. doi: 10.1038/35044558

Vasey, M. W., and Thayer, J. F. (1987). The continuing problem of false positives in repeated measures ANOVA in psychophysiology: a multivariate solution. *Psychophysiology* 24, 479–486. doi: 10.1111/j.1469-8986.1987.tb00324.x

Voss, M. W., Kramer, A. F., Basak, C., Prakash, R. S., and Robers, B. (2010). Are expert athletes 'expert' in the cognitive laboratory? A meta-analytic review of cognition and sport expertise. *Appl. Cogn. Psychol.* 24, 812–826. doi: 10.1002/acp.1588

Wang, C. H., Chang, C. C., Liang, Y. M., Chiu, W. S., Tseng, P., Hung, D. L., et al. (2013a). Open vs. closed sports and the modulation of inhibitory control. *PLoS One* 8:e55773. doi: 10.1371/journal.pone.0055773

Wang, C. H., Chang, C. C., Liang, Y. M., Shih, C. M., Muggleton, N. G., and Juan, C. H. (2013b). Temporal preparation in athletes: a comparison of tennis players and swimmers with sedentary controls. *J. Mot. Behav.* 45, 55–63. doi: 10.1080/00222895.2012.740522

Wang, C. H., Tsai, C. L., Tseng, P., Yang, A. C., Lo, M. T., Peng, C. K., et al. (2014). The association of physical activity to neural adaptability during visuo-spatial processing in healthy elderly adults: a mulitscale entropy analysis. *Brain Cogn.* 92, 73–83. doi: 10.1016/j.bandc.2014.10.006

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Technical and Interpretive Manual.* San Antonio, TX: Pearson.

West, R., and Moore, K. (2005). Adjustments of cognitive control in younger and older adults. *Cortex* 41, 570–581. doi: 10.1016/s0010-9452(08)70197-7

West, R., and Travers, S. (2008). Differential effects of aging on processes underlying task-switching. *Brain Cogn.* 68, 67–80. doi: 10.1016/j.bandc.2008.03.001

Wu, P. W. (2011). *A Study of the Relationships among Interpersonal Intimacy, Social Participation and Mental Health in Elders.* Unpublished master's dissertation, Taipei: National Taipei University of Education.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 21 August 2015
doi: 10.3389/fnbeh.2015.00228

Spontaneous movement tempo can be influenced by combining action observation and somatosensory stimulation

Ambra Bisio[1], *Laura Avanzino*[1], *Giovanna Lagravinese*[1,2], *Monica Biggio*[1,2], *Piero Ruggeri*[1] and *Marco Bove*[1]*

[1] *Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Genoa, Italy,* [2] *Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy*

OPEN ACCESS

Edited by:
Katiuscia Sacco,
University of Turin, Italy

Reviewed by:
Paul M. Nealen,
Indiana University of Pennsylvania, USA
Francesca Garbarini,
University of Turin, Italy

Correspondence:
Marco Bove,
Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Viale Benedetto XV 3, 16132 Genoa, Italy
marco.bove@unige.it

Received: *24 April 2015*
Accepted: *10 August 2015*
Published: *21 August 2015*

Citation:
Bisio A, Avanzino L, Lagravinese G, Biggio M, Ruggeri P and Bove M (2015) Spontaneous movement tempo can be influenced by combining action observation and somatosensory stimulation. Front. Behav. Neurosci. 9:228. doi: 10.3389/fnbeh.2015.00228

Spontaneous movement tempo (SMT) was a popular field of study of the Gestalt psychologists It can be determined from subjects freely tapping out a rhythm with their finger, and it has been found to average about 2 Hz. A previous study showed that SMT changed after the observation of rhythmical movements performed at frequency different from the SMT. This effect was long-lasting only when movement execution immediately followed action observation (AO). We recently demonstrated that only when AO was combined with peripheral nerve stimulation (AO-PNS) was it possible to induce plastic changes in the excitability of the motor cortex, whereas AO and PNS alone did not evoke any changes. Here we investigated whether the observation of rhythmical actions at a frequency higher than the SMT combined with PNS induced lasting changes in SMT even in absence of immediate movement execution. Forty-eight participants were assigned to four groups. In AO-PNS group they observed a video showing a right hand performing a finger opposition movement sequence at 3 Hz and contemporarily received an electrical stimulation at the median nerve; in AO group and PNS group participants either observed the same video or received the same electrical stimulation of the AO-PNS group, respectively; in LANDSCAPE group subjects observed a neutral video. Participants performed a finger opposition movement sequence at spontaneous movement rate before and 30 min after the conditioning protocols. Results showed that SMT significantly changed only after AO-PNS. This result suggested that the AO-PNS protocol was able to induce lasting changes in SMT due to neuroplasticity mechanisms, indicating possible application of AO-PNS in rehabilitative treatments.

Keywords: spontaneous movement tempo, action observation, peripheral nerve electrical stimulation, finger opposition movements, memory retention

Abbreviations: SMT, spontaneous movement tempo; AO, action observation; PNS, peripheral nerve stimulation; AO-PNS, action observation-peripheral nerve stimulation; TD, touch duration; ITI, inter-tapping interval.

Introduction

Rhythm and time play an essential role in many of the behaviors we engage in everyday life. Indeed, actions take place in a dynamic environment where successful interactions require a correct perception of how the action evolves in time. For that reason, an efficient representation of an action's temporal pattern is a prerequisite for appropriate reactive and proactive behaviour.

Although each individual has its own spontaneous and preferred rhythm, a number of voluntary movements show a common "spontaneous movement tempo" (SMT). SMT was a popular field of study of the Gestalt psychologists in the first half of the 20th century. It can be simply determined from subjects freely tapping out a rhythm with their hand or fingers (Vanneste et al., 2001; McAuley et al., 2006). McAuley et al. (2006) suggested that individual SMT refers to the rate of a putative endogenous oscillator. Further, behavioural measures demonstrated that SMT and preferred perceptual tempo are strongly correlated indicating this oscillator as a central mechanism (McAuley et al., 2006; Michaelis et al., 2014). As a consequence, SMT would not be merely confined to the motor domain but it would be the expression of an overall mechanism, which could influence the perception of time.

Bove et al. (2009) showed that SMT could be modified through action observation (AO). Indeed, the observation of repetitive finger opposition movements at a frequency different from the spontaneous one produced tempo's changes that closely resembled the observed rhythms and that were long-lasting. However, the observation–execution interval had a significant effect on learning: the larger was the interval between the observation and the first movement execution, the weaker was the effect on the SMT. Notably, when the motor task was executed for the first time 45 min after the video, there were no significant SMT changes. In general, it has been proposed that memory of the behavioural aspects of an observed rhythmical action can be formed only when movements are promptly executed after video observation (Zhang et al., 2011).

In a previous study (Bisio et al., 2015) we proposed an original stimulation paradigm where the observation of repetitive thumb-index tapping movements performed with the right hand was coupled with the right median nerve electrical stimulation at the level of the wrist (action observation—peripheral nerve stimulation, AO-PNS). AO-PNS induced an increase of the left primary motor cortex excitability in the muscle involved by the stimulations that was maintained up to 45 min after the stimulations, suggesting that the conditioning protocol was able to evoke neuroplastic changes at a cortical level. This study focused on a physiological marker of neuroplasticity (i.e., changes of corticomotor excitability) and it is currently unclear whether the cortical phenomena induced by this new multimodal training paradigm convey also modifications of the motor performance (Wenderoth, 2015). Theoretically, different aspects of movement kinematics can be changed by means of AO-PNS, including temporal patterns, as the SMT during motor performance. It could be hypothesized that the combination of AO and peripheral nerve stimulation (PNS) could induce a lasting modification of the SMT even in absence of voluntary movement execution. In other words, one could assume that the lasting changes in the cortical excitability following AO-PNS might be associated with modifications of the SMT. This would mean that AO-PNS is able to modify a behavioral response without requiring a movement execution.

To test this hypothesis, in the present study a group of participants was asked to perform a repetitive finger opposition movement sequence at spontaneous frequency before and 30 min after observing the same movements at 3 Hz (i.e., a frequency higher than the spontaneous one) and contemporarily receiving an electrical stimulation of the right median nerve (AO-PNS group). Results on movement's kinematics were compared with those obtained in other three control groups, which received AO and PNS alone (AO group and PNS group, respectively) or observed a video showing different landscape images (LANDSCAPE group).

Materials and Methods

Participants

Forty-eight participants (24 females and 24 males, mean age: 25.6 ± 4.3 years), naive to the purpose of the experiment, were recruited for this study. They reported no previous history of neurological disorders or orthopedic problems for the right-dominant hand—as determined by the Edinburgh Handedness Inventory (Oldfield, 1971), and they participated in this study after giving an informed consent. The experimental protocol was approved by the ethics committee of the University of Genoa and was carried out in agreement with legal requirements and international norms (Declaration of Helsinki, 1964).

Once enrolled, participants were randomly assigned to one of the four experimental groups: 12 participants (6 females and 6 males, mean age: 25.4 ± 4.1 years) joined the AO-PNS group whilst the remaining were divided in equal numbers in the three control groups: 12 (7 females and 5 males, mean age: 26 ± 4.8 years) to the AO group, 12 (6 females and 6 males, mean age: 25.2 ± 4.7 years) to the PNS group, and 12 (5 females and 7 males, mean age: 25.9 ± 4.1 years) to the LANDSCAPE group.

Study Design

Participants were seated in a comfortable chair in a quiet room and wore a sensor-engineered glove (Glove Analyzer System, GAS; ETT S.p.A., Italy) on their right hand. The glove is made in lycra and on the top of each finger conductive wires are placed to record the contact between the thumb and the other fingers. This system was previously used to study finger motor performance in both healthy subjects (Bove et al., 2009) and neurological patients (Bonzano et al., 2013; Pelosin et al., 2013). In the present study this system allowed the evaluation of the temporal properties of finger's movement. Participants were instructed to execute at spontaneous velocity two blocks, each one composed of five repetitive sequences of finger opposition movements: opposition of thumb to index, medium, ring and little fingers (PRE). Thus, each block consisted in a set of

20 individual movements, four in each sequence. An eyes-closed paradigm was chosen to avoid possible confounding effects due to the integration of external visual information. All the participants had a short familiarization session during which they had to perform one sequence at their spontaneous velocity.

Depending on the group, participants received one of the four different conditioning protocols. In AO-PNS group, participants were requested to look at a computer screen where a video showing a right hand performing repetitive finger opposition movements was displayed. This movie clip was obtained by filming on a black background the right hand of a human demonstrator who performed a finger opposition movements sequence (thumb towards index, middle, ring, and little fingers) paced with a metronome at 3 Hz. While observing the visual stimulus a total of 311 electrical stimuli (stimulation frequency 0.37 Hz) were delivered on the median nerve of the right wrist, for a total duration of 840 s (i.e., 14 min). This means that subjects observed 2520 finger opposition movements, grouped in a total of 630 sequences. The frequency of the electrical stimulation was set in order to administer to the subject an electrical stimulus every eight finger's opposition movement (in correspondence to the thumb-index closing phase), as already proposed in our previous study (Bisio et al., 2015). A MatLab custom-made software managed the synchronization between the video presentation and the electrical stimulations. Electrical stimuli were applied through a bipolar electrode (cathode proximal) connected to a Digitimer constant current stimulator (DS7AH HV, Digitimer Ltd., UK), using a square wave pulses (duration 1 ms) at an intensity of three times the perceptual threshold (Ziemann et al., 2004). To find the perceptual threshold the experimenter placed the electrode on the right wrist in a position corresponding to the median nerve location. The electrical stimulation was delivered at different intensities in a random order with the aim to find the lowest intensity perceived by the participant, who was verbally questioned by the experimenter. This value was considered the perceptual threshold. Then, the intensity of stimulation was increased to three times the perceptual threshold, intensity able to excite also the motor fibers of the mixed median nerve, i.e., to evoke a small twitch in the innervated muscle (abductor pollicis brevis). All subjects tolerated this intensity of stimulation. No audio accompanied the video presentation. Additionally, to keep participants attentive on the visual stimulus, a dot was superimposed for 1 s over the video. A total of 18 dots appeared on the screen during the video administration in a random position with respect to the depicted hand. Participants were asked three times, in a random instant of the video, to count the total number of dots appearing during video observation and the experimenter questioned them during the experiment. In AO group and PNS group the subjects either observed the same video (AO group) or received the same electrical stimulation (PNS group) of the AO-PNS group. To control for attention, participants in AO group counted the total number of dots appearing on the screen whereas participants in PNS group counted the total number of electrical stimulation they received. In the LANDSCAPE group participants looked at the computer screen where a sequence of landscape images alternated at random frequency. This condition was introduced to evaluate the potential kinematic effects due to the repetitions of the task. As in AO-PNS group and in AO group, participants had to count the total number of dots appearing on the screen. Participants were then kept relaxed in the laboratory for 30 min after the end of the conditioning protocol. In this period they were requested to read a book and not to train themselves in the motor task they previously performed. At the end of this period, they accomplished for a second time two blocks of five finger opposition movement sequences (POST; **Figure 1**).

Data Processing and Statistical Analysis

Data from glove were processed with a customized software (GAS, ETT, S.p.A., Italy). Touch duration (TD; i.e., the contact time between the thumb and another finger, ms) and inter-tapping interval (ITI; i.e., the time interval between the end of a thumb-to-finger contact and the beginning of the subsequent contact in the finger motor sequence, ms) were extracted from the acquired data. The software provided the mean values of the parameters for each block. Therefore, a single mean TD value and a single mean ITI value were provided for each block. TD and ITI were considered as outcome variables together with finger's movement rate, which was calculated as 1000/(TD + ITI) (Hz) (**Figure 2A**).

All the variables were normally distributed according to the *Shapiro-Wilk W test*. The mean values of the parameters over the blocks in PRE and POST epochs were submitted to the statistical analyses. Mixed-designed ANOVAs with EPOCH, as within subject factor (PRE, POST) and GROUP, as between subject factor (AO-PNS, AO, PNS, LANDSCAPE) were applied

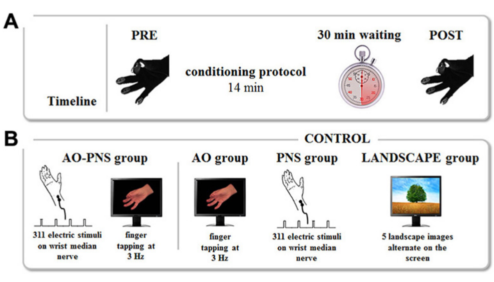


FIGURE 1 | Experimental protocol. (A) Timeline. The kinematics of finger opposition movements were tested before (PRE) and 30 min after (POST) each conditioning protocol by mean of a sensor-engineered glove. **(B)** Conditioning protocols. The experiment consisted of four conditioning protocols. During Action Observation-Peripheral Nerve Stimulation (AO-PNS) 311 electrical stimulations of the median nerve of the right wrist were administered to the participant while she/he was observing a video showing finger opposition movements paced at 3 Hz: opposition of thumb to index, medium, ring and little fingers. The electrical stimulation was delivered during the thumb-index closing phase. Action Observation (AO), Peripheral Nerve electrical Stimulation (PNS) and LANDSCAPE observation alone were here considered as control conditions. During AO and PNS the subjects either observed the same video (AO group) or received the same electrical stimulation (PNS group) of the AO-PNS group. During LANDSCAPE observation (LANDSCAPE group) participants looked at the computer screen where a sequence of landscape images alternated.

to evaluate the effect of the conditioning protocols on finger motor performance. Newmann-Keuls *post hoc* tests were used to explore significant interactions. Values are presented as means ± standard error.

Results

The main finding of the present study was that only subjects who received the AO-PNS protocol increased their SMT, whilst no modifications occurred in the three control groups. The single-subject movement rate values in PRE and POST epochs are quantified in **Figure 2B** together with the mean movement rate values.

Statistical analysis on movement rate showed a significant EPOCH*GROUP interaction ($F_{(3,44)} = 9.38$, $p < 0.001$). *Post hoc* comparisons revealed that before the conditioning protocols movement rate did not significantly differ among groups (PRE movement rate in AO-PNS: 2.07 Hz ± 0.07; AO: 2.04 Hz ± 0.07; PNS: 2.18 Hz ± 0.06 and LANDSCAPE: 1.94 Hz ± 0.06; p always >0.2).

Movement rate significantly increased 30 min after the conditioning protocol with respect to baseline only in the AO-PNS group (POST: 2.63 Hz ± 0.08, PRE vs. POST: $p = 0.0001$), whereas no significant differences were found when comparing PRE and POST values of movement rate in the other groups (in AO, PNS and LANDSCAPE, PRE vs. POST: p always <0.2). Accordingly, after the conditioning protocol (POST) movement rate values in AO-PNS group were significantly higher than those evaluated in AO group (2.26 Hz ± 0.08, $p = 0.009$); PNS group (2.23 Hz ± 0.08, $p = 0.01$) and LANDSCAPE group (1.91 Hz ± 0.08, $p = 0.0001$).

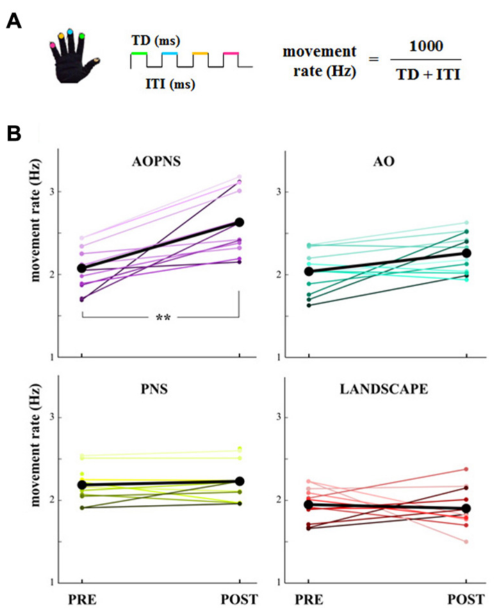


FIGURE 2 | Movement rate. (A) Finger-opposition movements sequence. The upper colored lines symbolize the touch duration (TD) and the lower black line stands for the interval between two consecutive finger opposition movement (inter-tapping interval, ITI). The colors code the finger. **(B)** Quantitative representation of the single-subject movement rate (Hz) in PRE and POST epochs (colored lines). Black lines show mean movement rate values for each experimental group: AO-PNS, AO, PNS and LANDSCAPE. **indicate significantly higher frequency in POST than PRE values ($p < 0.001$).

The mean values of TD and ITI are represented in **Figures 3A,B**, respectively. In the group of participants who experienced AO-PNS it is possible to observe a noticeable decrease of both TD and ITI values, differently to what happened in the groups who received the other conditioning protocols.

Statistical analysis showed a significant interaction (EPOCH*GROUP) for both TD ($F_{(3,44)} = 8.12$, $p < 0.001$) and ITI ($F_{(3,44)} = 3.77$, $p < 0.05$). *Post hoc* comparisons revealed no significant differences among groups in TD and ITI before the application of the conditioning protocols (PRE) (TD in AO-PNS: 226.03 ms ± 14.02; AO: 224.86 ms ± 10.57; PNS: 215.15 ms ± 8.59 and LANDSCAPE: 214.64 ms ± 18.52; p always <0.7; ITI in AO-PNS: 279.49 ms ± 16.64; AO: 289.29 ms ± 15.66; PNS: 257.65 ms ± 9.06 and LANDSCAPE: 325.87 ms ± 27.3; p always <0.2).

When comparing PRE and POST characteristics of finger opposition movements, among the different conditioning protocols tested, only AO-PNS was able to induce a significant decrease of TD (POST: 186.97 ms ± 9.28, $p = 0.0004$) and ITI (POST: 212.27 ms ± 11.88, $p = 0.0005$). Indeed we did not find any significant changes in TD and ITI when comparing PRE and POST in the AO (TD: 203.91 ms ± 12.02, $p = 0.09$; ITI: 253.59 ms ± 14.94, $p = 0.13$); PNS (TD: 209.6 ms ± 12.01, $p = 0.77$;

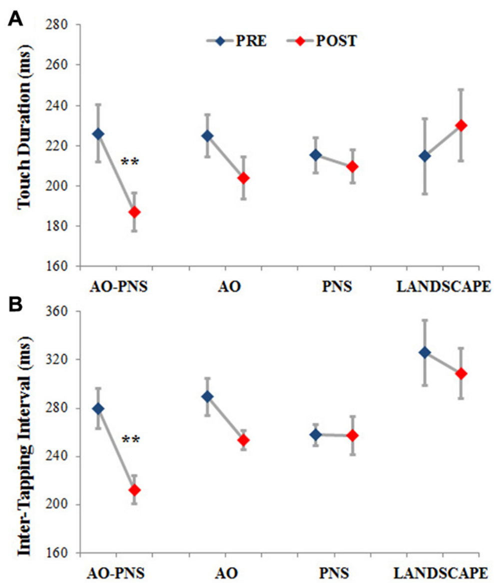


FIGURE 3 | Touch duration and inter-tapping interval. The TD **(A)** and the ITI **(B)** are represented for each experimental group before (PRE-blues) and 30 min after (POST-red) the conditioning protocol. Mean data ± standard error are shown; ** indicate significantly higher frequency in POST than PRE values ($p < 0.001$).

ITI: 257.46 ms ± 14.94, $p = 0.98$) and LANDSCAPE (TD: 230.04 ms ± 12, $p = 0.33$; ITI: 308.74 ms ± 14.95, $p = 0.25$) groups.

Discussion

The present study focused on the concept of SMT and on how SMT can change following a multimodal training paradigm. In particular, we explored whether AO combined with the peripheral nerve electrical stimulation was able to induce lasting modifications in SMT, even in absence of motor execution. Indeed, from previous studies, we already knew that AO *per se* is able to induce motor learning: i.e., lasting changes in motor performance (Bove et al., 2009; Zhang et al., 2011). However, these studies highlighted the crucial role played by motor execution in consolidating what has been learnt by means of AO. As an example, Bove and coworkers showed that immediately after AO participants' movement rate approached the rate of the observed movement. Instead, when participants were tested for the first time 45 min after AO, SMT did not change (Bove et al., 2009), suggesting that the absence of instant movement execution prevented the acquisition of the new temporal pattern.

In order to overcome this issue, in the present study a group of participants was required to perform a rhythmical finger opposition movement sequence at spontaneous velocity before and 30 min after observing the same movements at a frequency higher than the spontaneous one, and contemporarily receiving an electrical stimulation of the right median nerve (AO-PNS group). Results on movement's kinematic showed that participants' SMT was differently modulated by the different conditioning protocols. When AO was delivered together with peripheral nerve electrical stimulation (AO-PNS), it resulted in a global reorganization of the motor response: an increase in spontaneous movement rate that was due to both a decrease of TD and a decrease of ITI. Notably, this effect occurred 30 min after the end of AO-PNS protocol, despite the subjects were explicitly asked not to execute the observed action. This finding indicates that, even in absence of voluntary movement execution, it was possible to induce a lasting modification of the SMT, suggesting that AO-PNS not only affects motor cortex excitability (Bisio et al., 2015) but also motor response.

If we focus on the mechanisms that produced the observed modifications in SMT after AO-PNS, an intriguing finding is that both TD and ITI significantly contributed to this result. ITI is likely to represent a pure motor component of the whole motor task, whereas TD may be regarded as the combination of a sensory phase and a motor preparation phase in which the successive movement is correctly planned prior to the execution.

As concerns the decrease of the ITI, this might be caused by the automatic imitation of the observed movement rhythm: i.e., in order to increase movement speed the time spent to move from the contact of one finger to the subsequent one decreased. This result was shown also in the work of Pelosin and collaborators (Pelosin et al., 2013), where healthy adults and patients with Parkinson's disease received an AO paradigm. In that study the increase in spontaneous movement rate was caused by the reduction of ITI and the authors suggested that AO was able to provide information dealing with the dynamic part of movement (transition between a finger to the successive one). In the present work, AO training, as well as PNS and LANDSCAPE trainings, did not induce changes in ITI. The discrepancy between the present findings and those of Pelosin and coworkers (Pelosin et al., 2013) is likely to be due to the time interleaved between the training and the first movement execution. Indeed, the lack of an immediate comparison between the "observed" or visual and the "experienced" or somatosensory representations might have prevented the consolidation of the kinematic details of the observed motion.

Here the increase in spontaneous movement rate after AO-PNS was triggered also by the decrease of TD. The time of contact is the time to integrate the perceptual information and to plan the following movement. This result suggests that the plasticity evoked by AO-PNS is not limited to pure corticomotor mechanisms but rather involves also those cortical areas devoted to the processing of the sensory component of an action, leading to a sensorimotor plasticity. Therefore, not only sensory but also of frontal areas involved in motor planning should be activated by AO-PNS.

Participants' movement rate did not change after AO, PNS and LANDSCAPE protocols. This result was expected in the group that observed the alternation of landscape images since the video did not display movements or, in general, anything related to rhythm. In the matter of AO and PNS alone this finding is in line with our previous study, where we showed the absence of changes in cortical excitability after 14 min of either AO or PNS alone (Bisio et al., 2015).

As in our previous work (Bisio et al., 2015), the present findings highlight the main role of the somatosensory feedback during AO in evoking a modification of the response of the motor system, here proved by the changes of participants' SMT. We can speculate that, in the group who received AO-PNS, the peripheral electrical nerve stimulation consolidated the kinematic information acquired via AO, leading to the observed change of SMT. This modification might have occurred through the integration of the visual and the somatosensory information in M1. Indeed, AO activates the frontal part of the mirror neuron system that, in turn, activates M1 through cortico-cortical connections. Here, this activity would combine with that evoked by afferent information generated by PNS, leading to an enduring increase of M1 excitability (Bisio et al., 2015) and, in the present study, to the modification of SMT.

Several works focused on the application of AO as a tool to modify the spontaneous features of the human motor behavior in healthy subjects and neurological patients. These studies took advantage of the activity of the mirror neuron system, a neural circuit that is active during movement or passive observation of movement (Rizzolatti and Craighero, 2004). Most of them evaluated the effects on motor performance or on cortical activity evoked by the observation of movements combined with physical practice, where the latter could be executed simultaneously, as in the case of on-line motor imitation, or immediately after

AO, leading to an off-line imitative performance. For instance, when AO and physical practice were applied simultaneously it was shown that this combination was more effective to induce both plastic changes in primary motor cortex and motor performance improvements than physical practice or AO alone (Celnik and Cohen, 2004; Stefan et al., 2005, 2008; Celnik et al., 2006, 2008; Bove et al., 2009; Pelosin et al., 2013). Nevertheless, in these studies the first testing epoch immediately followed video observation. Therefore, one can conclude that, although participants motor performance might benefit from AO training, AO alone failed to induce long-term behavioral or cortical modifications, but might play a role in boosting the effects of physical practice (Stefan et al., 2005; Celnik et al., 2006). Alternatively, the information acquired via AO necessitates to be consolidated by the immediate movement execution (Bove et al., 2009).

A limitation of the present study is that a single test at 30 min after exposure was applied to verify the effects of A O-PNS on SMT. Nevertheless, since further evaluations might be conditioned by the previous movement execution, only the results of the first testing phase were considered representative of the behavioral outcome of AO-PNS. Future works will be devoted to test for how long the AO-PNS effects influence participant's motor response.

Conclusion

The connection between rhythm and movement dates back to Plato, who in *The Laws* defined rhythm as "the order in the movement". Nevertheless, rhythm is not only movement *per se* but it is related to how we experience and perceive the flow of events. The link between executed and perceived tempo has been established in works that considered not only continuous, rhythmical movement sequence (McAuley et al., 2006), but also the time perception of discrete, one-shot movements (Gavazzi et al., 2013). Indeed, these studies pointed out that SMT and preferred perceptual tempo are strongly correlated (McAuley et al., 2006) and that the closer is the perceived motion to the SMT, the lowest is the temporal error made during the reproduction of its duration (Gavazzi et al., 2013).

This study showed that the AO-PNS paradigm—which combines concurrent AO and peripheral nerve electrical stimulation—induces lasting modifications to the human motor behavior, here described as changes in SMT until 30 min after its application, without movement execution. These results add new insight concerning the effect of the combination of AO and PNS, a protocol already known to evoke plastic changes in the primary motor cortex excitability (Bisio et al., 2015). Therefore, we would like to propose that AO-PNS is able to tune the formation of a new motor memory where the temporal pattern are those acquired via AO and consolidated via PNS.

The present study opens new perspectives for developing multisensory clinical applications for those patients who cannot voluntarily move. Indeed, the possibility to train the motor system without moving represents an appealing way to restore the functioning of the motor cortical circuits and their abilities to plan a movement with non-pathological motor patterns, reestablishing, for instance, appropriate temporal properties. Then, giving the link between time perception and SMT, one could expect changes in the ability to perceive the temporal events. As consequence, we could speculate that the potential benefit adduced by an AO-PNS treatment would not be merely confined to the motor domain but would spread to perceptual mechanisms.

Particularly appealing is that AO-PNS is an easy-to-apply and cost-efficient intervention that can be performed unsupervised and might benefit patients with poor motor or cognitive abilities (Wenderoth, 2015).

References

Bisio, A., Avanzino, L., Gueugneau, N., Pozzo, T., Ruggeri, P., and Bove, M. (2015). Observing and perceiving: a combined approach to induce plasticity in human motor cortex. *Clin. Neurophysiol.* 126, 1212–1220. doi: 10.1016/j.clinph.2014.08.024

Bonzano, L., Sormani, M. P., Tacchino, A., Abate, L., Lapucci, C., Mancardi, G. L., et al. (2013). Quantitative assessment of finger motor impairment in multiple sclerosis. *PLoS One* 8:e65225. doi: 10.1371/journal.pone.0065225

Bove, M., Tacchino, A., Pelosin, E., Moisello, C., Abbruzzese, G., and Ghilardi, M. F. (2009). Spontaneous movement tempo is influenced by observation of rhythmical actions. *Brain Res. Bull.* 80, 122–127. doi: 10.1016/j.brainresbull.2009.04.008

Celnik, P. A., and Cohen, L. G. (2004). Modulation of motor function and cortical plasticity in health and disease. *Restor. Neurol. Neurosci.* 22, 261–268.

Celnik, P., Stefan, K., Hummel, F., Duque, J., Classen, J., and Cohen, L. G. (2006). Encoding a motor memory in the older adult by action observation. *Neuroimage* 29, 677–684. doi: 10.1016/j.neuroimage.2005.07.039

Celnik, P., Webster, B., Glasser, D. M., and Cohen, L. G. (2008). Effects of action observation on physical training after stroke. *Stroke* 39, 1814–1820. doi: 10.1161/strokeaha.107.508184

Gavazzi, G., Bisio, A., and Pozzo, T. (2013). Time perception of visual motion is tuned by the motor representation of human actions. *Sci. Rep.* 3:1168. doi: 10.1038/srep01168

McAuley, J. D., Jones, M. R., Holub, S., Johnston, H. M., and Miller, N. S. (2006). The time of our lives: life span development of timing and event tracking. *J. Exp. Psychol. Gen.* 135, 348–367. doi: 10.1037/0096-3445.135.3.348

Michaelis, K., Wiener, M., and Thompson, J. C. (2014). Passive listening to preferred motor tempo modulates corticospinal excitability. *Front. Hum. Neurosci.* 8:252. doi: 10.3389/fnhum.2014.00252

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Pelosin, E., Bove, M., Ruggeri, P., Avanzino, L., and Abbruzzese, G. (2013). Reduction of bradykinesia of finger movements by a single session of action observation in Parkinson disease. *Neurorehabil. Neural Repair* 27, 552–560. doi: 10.1177/1545968312471905

Rizzolatti, G., and Craighero, L. (2004). The mirror-neuron system. *Annu. Rev. Neurosci.* 27, 169–192. doi: 10.1146/annurev.neuro.27.070203.144230

Stefan, K., Classen, J., Celnik, P., and Cohen, L. G. (2008). Concurrent action observation modulates practice-induced motor memory formation. *Eur. J. Neurosci.* 27, 730–738. doi: 10.1111/j.1460-9568.2008.06035.x

Stefan, K., Cohen, L. G., Duque, J., Mazzocchio, R., Celnik, P., Sawaki, L., et al. (2005). Formation of a motor memory by action observation. *J. Neurosci.* 25, 9339–9346. doi: 10.3410/f.1029574.346435

Vanneste, S., Pouthas, V., and Wearden, J. H. (2001). Temporal control of rhythmic performance: a comparison between young and old adults. *Exp. Aging Res.* 27, 83–102. doi: 10.1080/036107301750046151

Wenderoth, N. (2015). Changing the brain with multimodal mirrors: combiningk visual and somatosensory stimulation to enhance motor plasticity. *Clin. Neurophysiol.* 126, 1065–1066. doi: 10.1016/j.clinph.2014.09.024

Zhang, X., de Beukelaar, T. T., Possel, J., Olaerts, M., Swinnen, S. P., Woolley, D. G., et al. (2011). Movement observation improves early consolidation of motor memory. *J. Neurosci.* 31, 11515–11520. doi: 10.1523/jneurosci.6759-10.2011

Ziemann, U., Ilić, T. V., Pauli, C., Meintzschel, F., and Ruge, D. (2004). Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J. Neurosci.* 24, 1666–1672. doi: 10.1523/jneurosci.5016-03.2004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs?

*Vânia de Aguiar[1,2,3], Roelien Bastiaanse[3], Rita Capasso[4], Marialuisa Gandolfi[5,6], Nicola Smania[5,6], Giorgio Rossi[7] and Gabriele Miceli[2]**

[1] International Doctorate in Experimental Approaches to Language And Brain (IDEALAB, Universities of Trento, Groningen, Potsdam, Newcastle and Macquarie University), Rovereto, Italy, [2] Center for Mind/Brain Sciences and Center for Neurocognitive Rehabilitation, University of Trento, Rovereto, Italy, [3] Center for Language and Cognition Groningen, University of Groningen, Groningen, Netherlands, [4] S.C.A. Associates, Rome, Italy, [5] Neuromotor and Cognitive Rehabilitation Research Centre, USO Neurological Rehabilitation, Azienda Ospedaliera Universitaria Integrata (AOUI) of Verona, Verona, Italy, [6] Department of Neurological and Movement Sciences, University of Verona, Verona, Italy, [7] Neurology, Santa Maria del Carmine Hospital, Rovereto, Italy

Background: Aphasia therapy focusing on abstract properties of language promotes both item-specific effects and generalization to untreated materials. Neuromodulation with transcranial Direct Current Stimulation (tDCS) has been shown to enhance item-specific improvement, but its potential to enhance generalization has not been systematically investigated. Here, we test the efficacy of ACTION (a linguistically motivated protocol) and tDCS in producing item-specific and generalized improvement in aphasia.

Method: Nine individuals with post-stroke aphasia participated in this study. Participants were pre-tested with a diagnostic language battery and a cognitive screening. Experimental tasks were administered over multiple baselines. Production of infinitives, of finite verbs and of full sentences were assessed before and after each treatment phase. Nonword repetition was used as a control measure. Each subject was treated in two phases. Ten daily 1-h treatment sessions were provided per phase, in a double-blind, cross-over design. Linguistically-motivated language therapy focusing on verb inflection and sentence construction was provided in both phases. Each session began with 20 min of real or sham tDCS. Stimulation site was determined individually, based on MRI scans.

Results: Group data showed improved production of treated and untreated verbs, attesting the efficacy of behavioral treatment, and its potential to yield generalization. Each individual showed significant item-specific improvement. Generalization occurred in the first phase of treatment for all subjects, and in the second phase for two subjects. Stimulation effects at the group level were significant for treated and untreated verbs altogether, but a ceiling effect for Sham cannot be excluded, as scores between real tDCS and Sham differed only before treatment.

Conclusion: Our data demonstrate the efficacy of ACTION and suggest that tDCS may enhance both item-specific effects and generalization.

Keywords: aphasia rehabilitation, verb retrieval, argument structure, sentence production, generalization, linguistically motivated therapy, transcranial direct current stimulation (tDCS), neuromodulation

OPEN ACCESS

Edited by:
Benedetto Sacchetti, University of Turin, Italy

Reviewed by:
Raffaella Ricci, University of Turin, Italy
Gesa Hartwigsen, Christian-Albrecht-University Kiel, Germany

****Correspondence:***
Gabriele Miceli, Center for Mind/Brain Sciences, University of Trento, Palazzo Fedrigotti - Corso Bettini 31, 38068 Rovereto, Italy
gabriele.miceli@unitn.it

Received: *23 April 2015*
Accepted: *07 July 2015*
Published: *30 July 2015*

Citation:
de Aguiar V, Bastiaanse R, Capasso R, Gandolfi M, Smania N, Rossi G and Miceli G (2015) Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs? Front. Behav. Neurosci. 9:190. doi: 10.3389/fnbeh.2015.00190

Introduction

Aphasia is an acquired language disorder that occurs following brain damage, frequently caused by stroke, traumatic brain injury or brain tumors. Though different rehabilitation strategies have been used in aphasia, they all share the general aim of improving communication. Currently available evidence indicates that aphasia therapy is effective (Brady et al., 2012). Nevertheless, 43% of the individuals with aphasia who suffer from language disorders due to a first-ever stroke are still aphasic 18 months post-onset (Laska et al., 2001). While most research on aphasia therapy focuses on the recovery of nouns, there is an increasing interest in the rehabilitation of verb and sentence production (Webster and Whitworth, 2012). Research addressing how to optimize verb and sentence rehabilitation programs to produce larger item-specific effects and generalization is needed. A recent addition to treatment tools for aphasia rehabilitation is tDCS—a neuromodulation technique introduced to increase treatment efficacy, in combination with Speech-Language Therapy. tDCS may enhance item-specific improvement, and it seems to be effective across a variety of tasks (de Aguiar et al., 2015).

The current study has three main goals. First, to test the efficacy of the Italian version of ACTION, a treatment protocol shown to result in generalization (Bastiaanse et al., 2006; Links et al., 2010). We focus specifically on verb retrieval and inflection in sentence production, and assess the effects of treatment on both treated and untreated verbs. Second, to test the potential of tDCS in enhancing both item-specific improvement and generalization, when paired with ACTION. Third, to discuss individual outcomes in relation to group results, in order to better understand the effects of a treatment combining tDCS and ACTION. In this introduction, we describe the cognitive processes involved in verb and sentence production, and we provide an overview of studies focusing on the treatment of verb and sentence production, and of studies using tDCS.

Verb and Sentence Production

A unique feature of lexical representations of verbs is that, contrary to most nouns, they contain information about argument structure that is necessary for sentence production (Saffran et al., 1980). This means that deficits in verb processing may contribute to deficits in sentence processing (e.g., patient HW, Caramazza and Hillis, 1991), though sentence-level deficits may also arise from other types of impairment. The speech-error model (Garrett, 1980) defines 3 processing levels involved in producing sentences. The *message level* entails the speaker's communicative goal and is a nonlinguistic representation of the idea to be conveyed by the speaker. This idea becomes semantically and thematically specified at the *functional level*. Here, semantic word representations are retrieved, the predicate-argument structure of the main verb specifies the number of arguments and the thematic roles required by the verb, and thematic roles are assigned to semantic representations (Schwartz, 2013). Inflectional affixes are included in this syntactic frame (Garrett, 1980). Finally, sentence constituents are ordered, and phonologically specified representations (lexemes) are retrieved from the phonological output lexicon, at the *positional level*. With languages having a limited amount of possible predicate argument structures, there is evidence that different verbs share combinatorial nodes (i.e., the stored information about the syntactic structures in which they occur; Pickering and Branigan, 1998) and that recent exposure to a sentence structure may facilitate the production of the same structure with a different verb (a phenomenon known as structural priming; Bock, 1986).

Even though these levels are conceived of as distinct processing stages, interactions between them are also assumed. For instance, after a syntactic frame is specified, some lexemes are more likely to be activated, due to their relation to appropriate semantic features (Bock, 1986). In addition, evidence for a relation between verb inflection and retrieval was reported by Bastiaanse (2011): individuals with fluent aphasia performed below norm in verb retrieval when producing finite verbs, but they were unimpaired when producing infinitives. Hence, syntax can influence lexical verb retrieval, due to both introduced lexical selection biases, and increased task complexity.

The neural correlates of these processes have been investigated in neuro-imaging research. Verb naming has been associated with activity in dorsolateral frontal and lateral temporal cortex (Perani et al., 1999), left frontal operculum and posterior middle temporal gyrus (Tranel et al., 2005). The processing of argument structure recruits left IFG (Inferior Frontal Gyrus) including BA47 and BA9, but also the superior temporal (Shetreet et al., 2007), angular and supra-marginal gyri and precuneus, which are more active in processing transitives than intransitives (Den Ouden et al., 2009). Thematic role assignment involves posterior perisylvian areas (Thompson et al., 2007). Tense inflection activates Broca's area, for both regular (e.g., Tyler et al., 2005) and irregular verbs (e.g., de Diego Balaguer et al., 2006). Kielar et al. (2011) report additional involvement of motor, premotor and posterior parietal regions in (overt and covert) present and past tense production. Each of these processes may be selectively impaired when the corresponding neural substrate is damaged, resulting in different sentence production deficits.

Rehabilitation of Verb and Sentence Production

The interest in the rehabilitation of verb production has increased over the last decades. At the single-word level, verbs can be treated with the same techniques used for nouns, even though improvement in verb production seems more difficult to achieve (Webster and Whitworth, 2012). At the sentence level, treatment techniques typically include identifying the agent and theme of each verb and then producing a sentence including all elements, thereby engaging predicate-argument structure retrieval and thematic role assignment. Aphasic individuals who underwent this type of treatment improved in retrieving treated, but not untreated verbs and showed improvement also in spontaneous speech (Fink et al., 1992; Webster et al., 2005). This suggests that verb production in sentence context may be a more productive treatment strategy than the production of verbs as isolated words. Research with sentence-level treatment has also led to the hypothesis that training complex syntactic structures results in generalization to untrained, linguistically-related, less complex structures (Complexity Account for Treatment Efficacy, Thompson et al., 2003). In line with this hypothesis, treating three-argument verbs in sentence production improved retrieval of untreated one- and two-argument verbs (Thompson et al., 2013).

A linguistically-motivated treatment protocol has been designed to address both lexical-semantic (argument structure) and syntactic (movement) properties of verbs (Treatment of Underlying Forms; Thompson and Shapiro, 2005). This treatment starts by addressing knowledge of/access to the thematic information of verbs. Aphasia patients are subsequently made aware of the properties of movement operations, in an explicit way. The benefits of treatment were shown to generalize to (less complex) constructions requiring the same type of movement as those treated explicitly, and to spontaneous speech (e.g., Thompson et al., 1996), in line with the Complexity Account for Treatment Efficacy (Thompson et al., 2003).

Two studies report on the treatment of verbal morphology by means of a Computerized Visual Communication protocol (Weinrich et al., 1997, 1999). This treatment was used to elicit past, present and future tense forms of regular and irregular verbs in sentences. In both studies, the production of inflected verbs in sentences improved, and generalization was observed in the use of morphological transformations, but not in verb retrieval.

Notably, generalization to lexical retrieval of untreated verbs occurs infrequently (Webster and Whitworth, 2012). The occurrence of generalization may depend on patient characteristics and treatment characteristics. Individuals with semantic damage may be more likely to generalize if treatment restores semantic features that are shared across semantic representations of words. Lexical representations, however, are item-specific and patients with lexical damage are therefore less likely to generalize (Miceli et al., 1996). In what concerns treatment tasks, for nouns, treatments for semantic processing is thought to have greater potential to induce generalization, due to the large overlap of semantic features across words of the same semantic category (e.g., Boyle and Coelho, 1995). However, the same strategy produces only item-specific improvement in verb retrieval (Wambaugh and Ferguson, 2007; Wambaugh et al., 2014).

ACTION is a treatment protocol for aphasia rehabilitation developed for Dutch (Bastiaanse et al., 1997). It includes four steps that address the different levels of processing necessary for producing verbs in simple, declarative sentences:

(1) Step 1, lexical level: action naming
(2) Step 2, syntactic level: sentence completion with a verb in the infinitive
(3) Step 3, morphosyntactic level: sentence completion with finite verb
(4) Step 4, sentence construction

In Bastiaanse et al. (2006), treating infinitives did not result in generalization, but treating finite verbs did. Links et al. (2010) found that, when infinitives were treated, untrained infinitives improved only marginally, and untrained finite verbs did not improve. By contrast, when finite verbs were treated, generalization was present for untreated finite verbs, but not for infinitives. Notably, improvement extended to spontaneous speech and to a task tapping communication in daily living, and was sustained after 3 months.

Altogether, the literature shows that when verbs are treated as isolated words, item-specific improvement can be achieved using similar techniques to those used for noun rehabilitation. Generalization to untreated verbs was reported following semantic, gestural and repetition cueing (Rose and Sussmilch, 2008), when treatment was centered at the sentence level and the grammatical properties of verbs were taken into account in designing the treatment task (Bastiaanse et al., 2006; Links et al., 2010; Thompson et al., 2013). These studies share two features—treatment addressed grammatical properties of verbs (e.g., argument structure, inflection, movement) and focused on the sentence level. Engaging knowledge of these abstract properties may be an important ingredient to achieving generalization.

tDCS in Aphasia Rehabilitation

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique. A weak electrical current is delivered through electrodes positioned over the scalp (e.g., Nitsche et al., 2008). In language research, studies with healthy individuals show that anodal tDCS can increase speed (Fertonani et al., 2010) and amount of verbal learning (Meinzer et al., 2014). Cathodal tDCS, on the other hand, negatively affected learning in an action and object learning paradigm (Liuzzi et al., 2010). In aphasia rehabilitation, methodology varies substantially across studies. Positive effects were reported in spite of variations in current intensity (1–2 mA), stimulation polarity and montage (perilesional cathodal tDCS in Monti et al., 2008; perilesional anodal in Baker et al., 2010; contralesional cathodal tDCS in Flöel et al., 2011 and contralesional anodal tDCS in Vines et al., 2011) (for reviews, see Hamilton et al., 2011; Monti et al., 2013; de Aguiar et al., 2015).

Models of inter-hemispheric competition (Murase et al., 2004) predict bicephalic montages (a perilesional anode and a contralesional cathode) to modulate interhemispheric interactions more efficiently than monocephalic montages (a perilesional anode and a reference electrode). Recently, it has been suggested that the optimal montage should be determined individually, based on lesion site and size (Hamilton et al., 2011) and the individuals' pattern of activation during correct language production (Baker et al., 2010).

Effective tDCS-related treatment enhancement may depend on appropriately pairing stimulation site and treatment task. Marangolo et al. (2013a, 2014) found that action naming and discourse cohesion were enhanced after stimulation to Broca's but not Wernicke's area[1]. Given that ongoing computations may depend on the pattern of cognitive impairments and brain damage, different patients may respond differently to tDCS. Currently, the lack of data on individual outcomes in many studies (except Marangolo et al., 2013a, 2014), and lack of detailed information about the linguistic deficits of participants do not allow establishing whether some treatments were more

[1]Given that electrodes of the same size were used over left and right hemisphere areas, the studies of Marangolo et al. (2013a, 2014) provide evidence for the efficacy of a bi-cephalic montage with anode over peri-lesional and cathode over contro-lesional areas. For a more detailed discussion see de Aguiar et al. (2015).

effective than others, as a function of lesion site and of cognitive impairment. Supporting the need to report individual outcomes, recent research with healthy participants identified a large variability in individual responses to stimulation (Horvath et al., 2014).

There is little information about the role of tDCS in promoting generalization. Some studies report a transfer to spontaneous speech (Marangolo et al., 2013b, 2014), and statistically insignificant increase of accuracy for untreated nouns (Baker et al., 2010). Nevertheless, in these studies pre-treatment performance was not measured in multiple baselines gathered in a time window similar to that of treatment. In addition, no control task was administered to ensure that behavioral improvement was specific to treatment-related tasks. Therefore, it is not possible to measure the potential effect of task practice nor to rule out spontaneous recovery (Howard et al., 2015). It is relevant to note that generalization could be expected to occur in conversational therapy (Marangolo et al., 2013b, 2014) due to the functional scope of treatment, but it was unlikely in picture-word matching (Baker et al., 2010). To assess the potential of tDCS in enhancing generalization, it is important to pair it with a treatment task likely to yield generalization (e.g., semantic feature analysis for nouns, or linguistically motivated therapies for verbs, such as Treatment of Underlying Forms or ACTION).

As mentioned earlier (Section Rehabilitation of Verb and Sentence Production), generalization in verb production has been observed infrequently. Treatment at the sentence level engaging knowledge of morphosyntactic properties of verbs appears to be effective with this regard, but studies reporting on generalized effects of verb treatment usually focus either on tense training or on argument structure training. In this study, we test the efficacy of the Italian adaptation of the ACTION protocol that combines training of lexical verb retrieval and of verbal morphology, in sentence context. This training should improve lexical retrieval of both treated and untreated verbs. In addition, here we test for the first time whether tDCS, in combination with speech/language therapy, can enhance both item-specific improvement and generalization.

Method

Recruitment and Participants

The main inclusion criterion was a difficulty in verb retrieval and sentence construction. Eligible participants were nine right-handed[2] individuals with chronic aphasia after a left hemisphere stroke, aged between 18 and 80 years and with at least 5 years of education. Seven participants presented with their first-ever stroke. The two participants who had had prior lesions were assigned to distinct treatment groups (sham-first and tDCS first). Exclusion criteria were sensitive skin, epileptic seizures in the 6 months preceding enrollment, use of drugs known to increase the risk of seizures and presence of metallic fragments in the head. The study was approved by the ethics committee of the University of Trento (protocol number 2012-035). After being referred by their neurologist, patients and primary caretakers were invited for a briefing session. In this session the procedure was described, and informed written consensus was obtained. **Table 1** provides a summary of participants' demographic and clinical characteristics. Detailed information about lesion sites is provided in Supplementary Materials.

Procedure

Prior to the beginning of the experimental protocol, participants were engaged in a diagnostic assessment. A multiple-baseline, double-blind and sham-controlled, cross-over design was used to assess treatment effects. The entire experimental protocol lasted 10 weeks (**Figure 1**). There were three assessment phases (baseline, intermediate and final), and two treatment phases. In each assessment phase, three testing sessions were spread over a period of 2 weeks, to encompass an interval similar to that of treatment[3]. They served to establish pre-treatment stability in primary outcome and control measures. This allowed to control (unlikely) effects of spontaneous recovery on the changes observed after treatment. In addition, the data from the three sessions that preceded each treatment phase were

[2]Handedness was reported in the neurological assessment of each patient, and confirmed by patient and/or caregiver.

[3]Patients PG and GD were tested in consecutive days because they had to travel to participate in the study.

TABLE 1 | Demographic and clinical characteristics of participants.

	Participant	Gender	Age	Han.	Education	Occupation	Lesion type	TPO
Sham first	LF	M	45	Right	High school	Tinsmith	Ischaemic	39
	GC	M	68	Right	Junior high school	Social worker	Ischaemic	26
	GD	F	48	Right	University degree	Accountant	Hemorrhagic	17
	GP	M	52	Right	High school	Retired	Ischaemic	80
	EC	M	54	Right	High school (incomplete)	Marble worker	Ischaemic	92
tDCS first	SP	M	75	Right	University degree	Accountant	Ischaemic	8
	RL	F	43	Right	High school	Accountant	Ischaemic	88
	CK	F	76	Right	Junior high school	Secretary	Hemorrhagic	54
	PG	M	52	Right	University degree	Insurance actuary	Ischaemic	36

Han., Handedness; TPO, Time Post-Onset (in months).

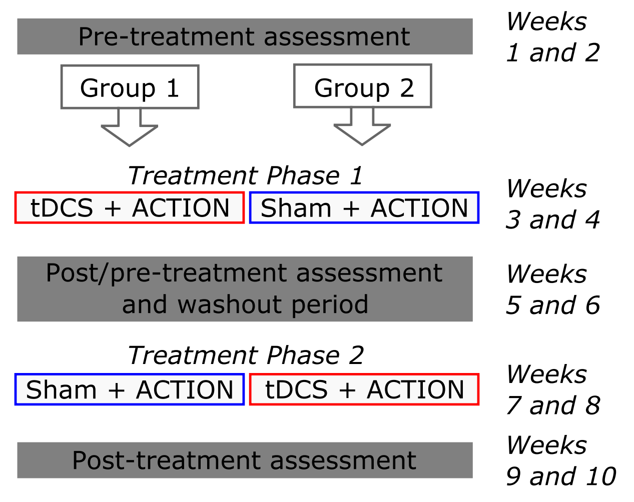


FIGURE 1 | Treatment study design. Each patient was involved in two treatment phases. Initially, participants were randomly assigned to one of two treatment orders. The entire protocol lasted 10 weeks.

used to construct two matched sets of verbs: one to be treated, one to measure generalization[4]. The scores obtained in the three pre-treatment assessment sessions were contrasted with those observed in the three post-treatment assessment sessions, to evaluate the effects of treatment on treated and untreated verbs, for each phase. Ten daily (five times per week) 1-h treatment sessions were provided in each treatment phase. Speech-Language Therapy was administered using the Italian version of the ACTION protocol (based on Links et al., 2010), described below. ACTION was administered in both phases, to each individual. Participants were randomly assigned to two possible treatment orders: 5 received Sham in the first, and tDCS in the second treatment phase; 4 received treatment in the reverse order.

Diagnostic Assessment

A diagnostic language battery (Batteria per l'Analisi dei Deficit Afasici, BADA, Miceli et al., 2006) was administered to identify the functional locus of language impairment. Additional tests for cognitive screening were administered, including Digit Span (Orsini et al., 1987), Clock Drawing (Dal Pan et al., 1989), and Attentive Matrices (Spinnler and Tognoni, 1987).

Tests Administered in Each Session of Each Assessment Phase

Three verb production tests were developed to assess changes in verb retrieval accuracy. Black-and-white line drawings were used to elicit the verb, in all tests (for examples, see **Figure 2**). In the first task (henceforth, VTinfinitives), participants were asked to complete a sentence (e.g., "L'uomo vuole…," The man wants…) with the corresponding verb in the infinitive ("…mangiare," to eat). In the second (henceforth, VTfinite), the to-be-completed sentence included a temporal adverb (e.g., "Ieri/Oggi/Domani l'uomo…," Yesterday/Now/Tomorrow the man…) and the patient had to produce the finite verb in the correct tense ("…ha mangiato/mangia/mangerà," ate, eats, will eat). In the third test (henceforth, VTsentence), the patient was prompted with the image, and asked to produce a Subject-Verb-Object (SVO, for transitive verbs, e.g., "L'uomo mangia la torta," The man eats the pie) or a Subject-Verb-Adjunct (SVA, for intransitive verbs, e.g., "L'uomo corre sulla spiaggia," The man runs at the beach). The adjunct was always a prepositional phrase expressing location. A complex scoring procedure was developed, but in this report only lexical accuracy is considered—a measure shared by the three verb tests. Responses were scored as correct if the patient produced the correct verb. Phonemic and morphosyntactic errors were disregarded.

The same 88 verbs were used in the three verb production tests. They were divided in three sets (sets 1, 2, and 3). In session 1 of each phase, set 1 was used for VTinfinitive, set 2 for VTfinite and set 3 for VTsentence. In sessions 2 and 3, the three sets were assigned to the three tasks using a Latin Square design. The three sets were matched for relative frequency, length in phonemes, number of internal arguments, instrumentality, name relatedness, body part involved (face, arm, leg), manipulation, inflectional paradigm and regularity. The comparison of lexical accuracy for 88 verbs across the three sessions that preceded each treatment phase allowed establishing pre-treatment stability.

Comprehension of these verbs was assessed using a picture verification test. The picture of a target verb was presented while the examiner pronounced a verb in the infinitive. The verb could be the target, a semantic distractor or an unrelated distractor (e.g., the picture corresponding to the verb "to eat" was paired, on different occasions, to the correct word "to eat," to the semantic foil "to drink" and to the unrelated foil "to mop"). On each day, 1/3 of the items was presented with the correct target, and the remaining 2/3 with distractors. Participants had to reply "yes" or "no" (verbally or by pressing a key) to indicate whether the verb presented auditorily corresponded to the picture. Targets, semantic and unrelated distractors were matched for frequency, length in phonemes, name relatedness, number of internal arguments, instrumentality and manipulation.

Performance on the nonword repetition test from the BADA (Miceli et al., 2006) was used as a control measure. This allowed assessing whether any observed improvement was treatment-related (i.e., restricted to verb tasks, which were the focus of treatment), or aspecific (nonword repetition measures phonological abilities, but is unrelated to verb retrieval). The test included 36 items, ranging in length between 1 and 3 syllables.

Behavioral Treatment

In Italian, Subject-Verb-Object is the base word order in sentences. Inflected verbs occur in second position without overt movement. In this study, treatment was provided at the level of simple, declarative sentences, and a task specifically designed to

[4]Please note that the baseline phase is the same as the item selection phase. Had patients been tested only on difficult items, data would have been susceptible to the problem of regression to the mean. In our case, 88 verbs were tested in all assessments, even though at each treatment stage only 40 (20 treated and 20 untreated) were selected for statistical analyses. This approach allows an economic use of time, as only one pre-treatment phase is needed, and circumvents the problem of regression to the mean, making it possible to reliably assess both item-specific improvement and generalization (Howard et al., 2015).

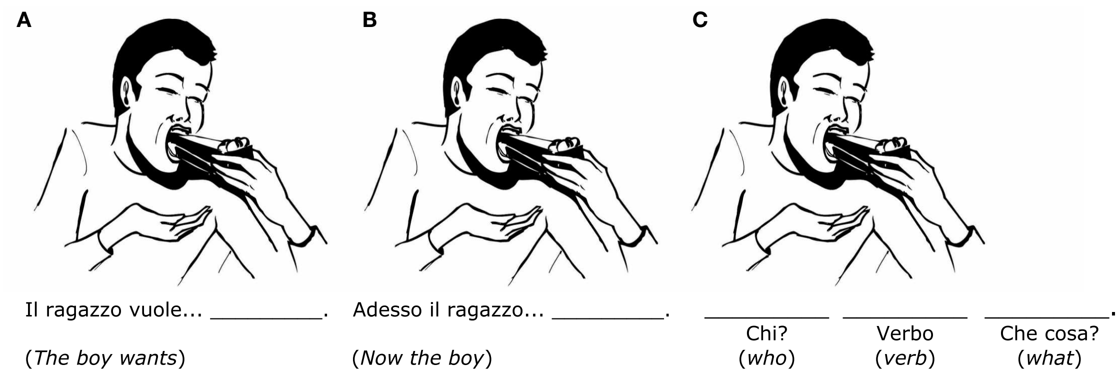


FIGURE 2 | Examples of stimuli used in the three verb production tests. (A) VTinfinitive (sentence completion with a verb in the infinitive). **(B)** VTfinite (sentence completion with a verb in the correct tense). **(C)** VTsentence (sentence construction).

address movement operations was not included. Considering the rich morphology of Italian, steps three and four used in ACTION for Dutch were modified to include verb production in three different tenses. The Italian adaptation of ACTION (Bastiaanse et al., 1997), includes these four steps:

(1) Step 1, lexical level: Action naming
(2) Step 2, syntactic level: Sentence completion with infinitive
(3) Step 3, morphosyntactic level: Sentence completion with finite verb in three tenses
(4) Step 4, Sentence construction with finite verb in three tenses

Therapy was provided over ten 1-h sessions in each phase. Each phase lasted 2 weeks and entailed treatment with two different tasks. Participants completed Step 3 in the first week, and Step 4 in the second week. Examples of stimuli for each step are provided in **Figure 3** (**Figures 3A,B** for Steps 3 and 4, respectively). In Step 3, the patient saw an image with an adverb and a subject written below the picture (e.g., "Now the man…"), and was asked to complete the sentence with the verb inflected in the correct tense. In Step 4, the patient saw an image and a written adverb (e.g., "now…"), and was requested to produce a full sentence that properly described the image (Subject-Verb-Object or Subject-Verb-Adjunct), with the verb inflected in the correct tense.

Structured increasing cues were provided. The cues provided to each subject depended on whether the participant produced retrieval errors or morphological errors, and on the constituent in which the error occurred. For a thorough description of the training procedure and of the cueing strategies provided during treatment steps three and four, the reader is referred to the Supplementary Material section. The 88 items included in ACTION were selected on the basis of a norming procedure. Ten healthy volunteers were asked to build sentences that described the picture stimuli. Items with less than 70% picture-sentence agreement across all constituents were excluded based on this data. The items surviving this procedure had a mean agreement of 90.11% (*sd* = 0.084%). In addition, these items were normed for a wide range of linguistic variables to create matched sets of verbs (Rofes et al., 2015).

For each participant, and prior to each treatment phase, two sets of 20 verbs were prepared: a to-be-treated set, to evaluate item-specific benefits of treatment, and a matched, not-to-be-treated set, to evaluate generalization to untreated items. Sets were matched for picture-sentence agreement, age of acquisition, imageability, relative frequency, length in phonemes, number of internal arguments, inflectional paradigm, instrumentality, name relatedness, manipulation, body part involved (face, arm, leg) using available norms (Rofes et al., 2015). In addition, to ensure comparability of treated and untreated items, the two sets were individually tailored. They were matched for retrieval accuracy across the three verb tasks in the three assessments that preceded each treatment phase, for error types produced by the patient, and for comprehension accuracy[5]. The details of set balancing for each patient are available as Supplementary Material.

tDCS

tDCS was administered using a battery-driven, programmable Eldith direct current stimulator (neuroConn, PLUS version), through two 35 cm^2 electrodes. Current intensity was increased in a ramp-like fashion for 5 s until reaching 1 mA (current density = 0.2 mA/cm^2). Each treatment session began with 20 min of real or sham bicephalic tDCS. Sham stimulation was administered with the same parameters used for real stimulation, but the stimulator was turned off after 30 s (Gandiga et al., 2006). The same procedure was repeated at the end of the 20-min period. To ensure blinding efficiency, participants were asked to fill a questionnaire at the end of each 2-week treatment phase (Fertonani et al., 2010), in which they indicated the nature and intensity of the sensations experienced during the treatment. Participants reported mild to moderate itchiness, pinching, burning, fatigue or heating under the electrode, mild pain. One patient reported mild headache and two others reported mild discomfort under the elastic strap.

Both the therapist who administered behavioral treatment and the experimenter who analyzed the data were blind to the

[5]Whenever possible, only verbs that the patient failed to name but comprehended correctly were included in the treatment and control sets (see Supplementary Materials for exact numbers). Exceptions were made only when fewer than 40 such verbs were available to prepare the two sets, due to poor comprehension.

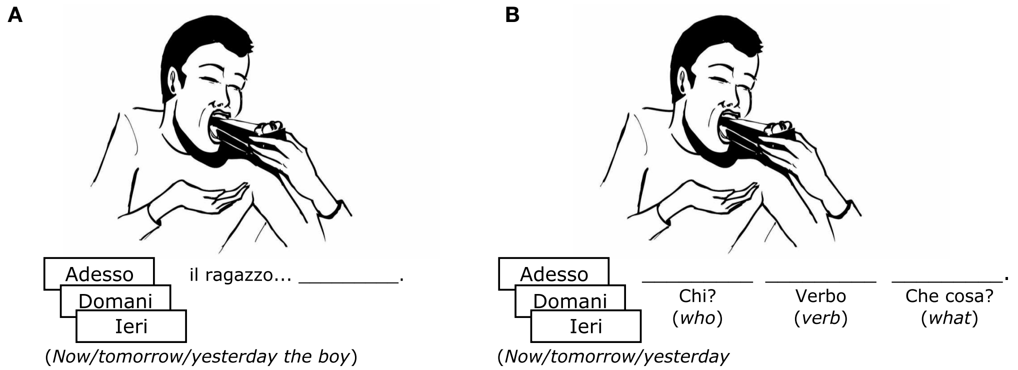


FIGURE 3 | Examples of stimuli used during treatment. (A) Step 3 (sentence completion with a verb in three tenses). **(B)** Step 4 (sentence construction in three tenses). Detailed information about cueing procedures for each step is available as Supplementary Materials.

TABLE 2 | Stimulation sites and electrode positioning.

	Anode (LH)	EEG coordinates	Cathode (RH)
LF	Anterior and superior to Broca's area (BA45-46)	Centered between F7 and F3	Homologous
GC	Superior/middle temporal gyri (BA21-22)	Centered between T7 and TP7	Homologous
GD	Broca's area (BA 44–45)	Crossing point between T3-Fz and F7-Cz	Homologous
GP	Superior/middle frontal gyri	Centered above FP1	Right Broca
EC	Anterior and superior to Broca's area (BA45-46)	Centered between F7 and F3	Homologous
SP	Superior/middle frontal gyri (BA10)	Centered above FP1	Right Broca
RL	Superior/middle frontal gyri (BA10)	Centered above FP1	Right Broca
KC	Broca's area (BA 44-45)	Crossing point between T3-Fz and F7-Cz	Homologous
PG	Broca's area (BA 44-45)	Crossing point between T3-Fz and F7-Cz	Homologous

EEG coordinates are expressed according to the international 10–20 system. LH, left hemisphere; RH, right hemisphere.

stimulation condition, until individual outcomes for phase 1 and 2 were statistically analyzed. A third experimenter handled the tDCS device in each treatment session. The difference in number and intensity of symptoms observed across tDCS and Sham phases was not significant (Wilcoxon Signed-Rank test = 0.84, $p = 0.200$, one tailed).

Stimulation site was determined individually, after inspection of each patient's MRI scan (see **Table 2**). The anode was always centered over a left perilesional area. In three participants (CK, PG and GD), this was Broca's area (BA 44–45), and in these cases the cathode was placed over the right hemisphere homolog of Broca's area. In two cases (LF and EC) the lesion partially encompassed Broca's area. In these subjects the anode was placed anterior and superior to Broca's area (BA45–46), and the cathode over the homologous area in the right hemisphere. In three other participants (GP, RL and SP) lesions were more anterior. Since they encompassed the entire IFG and caused considerable damage to the middle frontal gyrus, the anode was placed over the left superior and middle frontal gyri (BA9–10). In these cases, the cathode could not be positioned symmetrically, because shunting of current between electrodes (bypassing the brain) can occur with electrode distances under 8 cm (DaSilva et al., 2011). Therefore, the cathode was positioned over the right homolog of Broca's area. Finally, GC's lesion was parieto-occipital and parieto-temporal. In order to respect the rule of stimulating peri-lesional areas, the anode was positioned over the posterior middle and superior temporal gyri (encompassing Wernicke's area), and the cathode in a symmetrical position over the RH.

Broca's area was identified as the crossing point between T3-Fz and F7-Cz, following Friederici et al. (1998). All other coordinates were extracted from Okamoto et al. (2004), who studied the probabilistic mapping of 10-20 EEG coordinates and brain areas on the cortical surface.

Results

Diagnostic Assessment

Selected tests from the BADA (Miceli et al., 2006) were used to characterize the profile of language impairment in each subject. Results of this diagnostic assessment are presented in **Table 3**. Our sample included fluent (GC, GD, and PG) and nonfluent participants. In all cases, sentence production was characterized by omission of obligatory arguments, errors of thematic role assignment, morphological errors and difficulties in producing noncanonical sentences. Three participants had mild-to-moderate semantic impairment (GD, SP, and KC). All participants presented with damage to the phonological output lexicon. Different sublexical conversion mechanisms were impaired across subjects, but these always included phoneme-to-phoneme conversion. In addition, all participants

TABLE 3 | Scores (% error) in diagnostic assessment battery (BADA).

		Sham first					tDCS first			
		LF	GC	GD	GP	EC	SP	RL	CK	PG
Sublexical	Auditory discrimination	6.7	6.7	6.7	10.0	3.3	n.a.	10.0	10.0	3.3
	Visual-auditory discrimination	13.3	0.0	13.3	43.3	11.7	n.a.	20.0	n.a.	n.a.
	Nonword repetition	27.8	26.1	33.3	27.8	27.8	44.4	5.6	55.6	27.8
	Nonword reading	26.1	22.7	0.0	80.0	35.6	91.3	21.7	30.4	47.8
	Nonword writing	66.7	61.5	8.3	100.0	72.0	n.a.	41.7	75.0	41.7
	Nonword copy	50.0	n.a.	0.0	0.0	33.3	n.a.	0.0	16.7	16.7
Semantico-lexical	Auditory lexical decision	12.5	10.0	12.5	11.3	8.8	8.8	5.0	22.5	10.0
	Visual lexical decision	30.0	7.5	0.0	31.3	7.5	37.5	0.0	7.5	17.5
	Word repetition	27.3	0.0	4.5	2.2	2.2	55.6	9.1	4.5	27.3
	Word reading (aloud)	32.6	2.2	2.2	56.5	0.0	60.9	4.3	0.0	30.4
	Word writing to dictation	69.6	8.7	0.0	80.0	80.4	n.a.	8.7	17.4	17.4
	Word copy	40.0	20.0	0.0	20.0	40.0	100.0	0.0	0.0	40.0
	Auditory noun comprehension	10.0	2.5	20.0	2.5	0.0	30.0	0.0	5.0	0.0
	Visual noun comprehension	10.0	0.0	0.0	0.0	0.0	10.0	0.0	10.0	0.0
	Auditory verb comprehension	10.0	0.0	0.0	0.0	0.0	10.0	0.0	40.0	0.0
	Visual verb comprehension	10.0	5.0	0.0	30.0	0.0	40.0	0.0	30.0	0.0
	Oral object naming	66.7	20.0	60.0	16.7	43.3	60.0	0.0	13.3	33.3
	Written object naming	63.6	9.1	45.5	50.0	95.5	n.a.	27.3	18.2	36.4
	Oral action naming	71.4	28.6	57.1	78.6	57.1	64.3	0.0	14.3	42.9
	Written action naming	90.9	9.1	81.8	90.9	100.0	n.a.	27.3	36.4	54.5
Grammatical	Picture description—unconstrained	100.0	25.0	75.0	100.0	50.0	100.0	n.a.	100.0	100.0
	Picture description—constrained	100.0	70.0	80.0	100.0	80.0	100.0	n.a.	100.0	100.0
	Sentence repetition	40.0	30.0	10.0	60.0	5.0	n.a.	20.0	50.0	50.0
	Sentence reading	66.7	n.a.	0.0	100.0	0.0	n.a.	33.3	0.0	66.7
	Auditory comprehension	15.0	8.3	10.0	28.3	11.7	92.3	3.3	13.3	13.3
	Visual comprehension	26.1	3.3	13.0	26.7	4.4	n.a.	0.0	26.1	26.1

Underlined scores fall below norm.

presented with length-sensitive difficulties in tasks that required overt production, suggesting damage to phonological short-term memory. The diagnostic assessment of each patient is summarized in the Supplementary Materials.

Cognitive Screening

LF, GP, SP, RL, CK, and PG performed below norm in the forward Digit Span, consistent with reduced phonological short-term memory. All participants except RL performed below norm in digit span backwards. SP, KC and PG did not complete this task. Visual attention, as assessed by Attentive Matrices, was impaired in LF, GC, EC, SP, and RL. Visuo-spatial cognition and two-dimensional construction, as assessed by the Clock-Drawing test, was below norm in LF, EC, SP, and RL. Subject GD did not complete these two tasks, due to difficulties following instructions. Scores for each participant are presented in **Table 4**.

Group Results

Treatment Effects: Lexical Accuracy in Verb Production

Group data were analyzed by computing a generalized linear mixed model for logistic data, using model comparison to assess the need to include each factor (Jaeger, 2008). Models were computed using R package lme4 (Bates et al., 2014). The dependent variable was accuracy in verb production. Responses were scored as accurate if the target verb was produced, disregarding phonemic paraphasias and morphosyntactic errors. Pre-treatment stability was established by comparing accuracy between the three sessions that preceded each treatment phase, including all 88 verbs. For pre-treatment stability, the null model included random intercepts for Participants and Items. We tested this model against a model containing fixed effects for Session (assessment sessions 1, 2, and 3 prior to each treatment phase). The alternative model did not provide a better fit for the data in comparison to the null model in either phase 1 [$\chi^2(1) = 0.3512$, $p = 0.5534$] or phase 2 [$\chi^2(1) = 0.0708$, $p = 0.7902$], and the main effect of Session fell very far from significance (phase 1: $z = 0.593$, $p = 0.5530$; phase 2: $z = 0.266$, $p = 0.790$), showing stable behavior for this group of participants, before each treatment was administered (see **Figure 4A**).

Treatment outcome was established by computing a second model. The model included random intercepts for participants, with random slopes for Set*Time (Set = treated, untreated; Time = pre-, post-treatment), as patients may respond differently

TABLE 4 | Scores in cognitive screening tasks.

		Cut-off	Sham first					tDCS first			
			LF	GC	GD	GP	EC	SP	RL	CK	PG
STM and WM[1]	Forwards (0–8)	3.75	3.5	4.3	5.3	1.8	4.0	3.5	2.5	3.3	3.3
	Backwards (0–8)	5 ± 2	2.0	2.0	2.0	1.8	2.0	n.a.	4.0	n.a.	n.a.
Visual attention		31	27.3	23.0	n.a.	46.0	16.0	12.3	15.8	45.5	28.3
Visual-spatial cognition and two-dimensional construction		v.n. > 3	3.0	4.0	n.a.	5.0	3.0	-1.0	3.0	10.5	12.0

Digit Span (Orsini et al., 1987); Attentive matrices (Spinnler and Tognoni, 1987); Clock Drawing Test (Dal Pan et al., 1989). Underlined scores fall below norm.

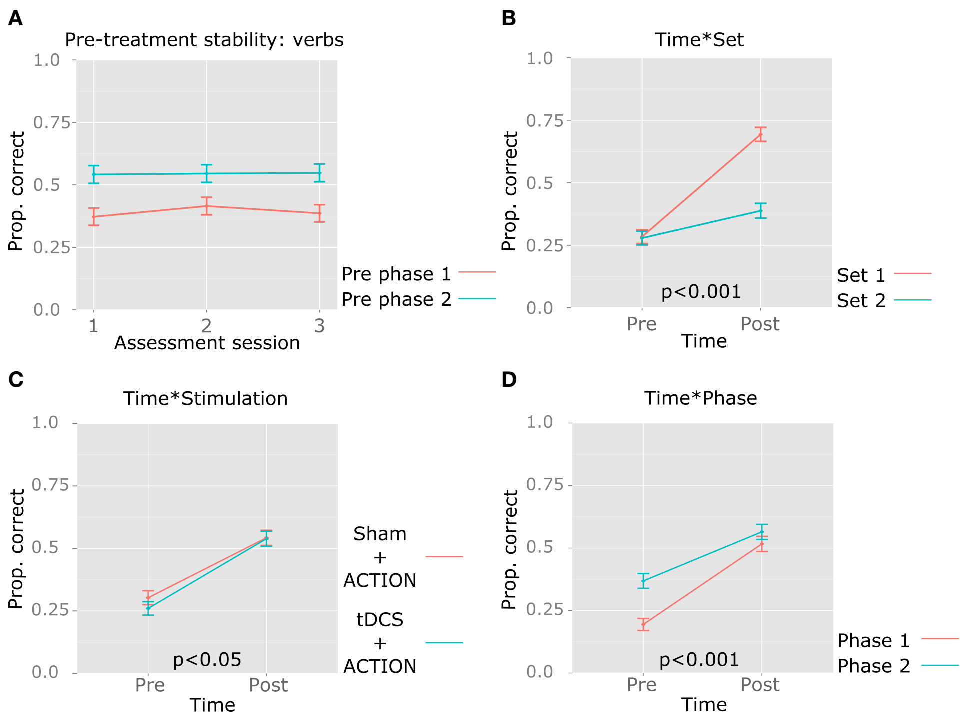


FIGURE 4 | Group results: pre-treatment stability and effects of treatment in verb retrieval. The mean proportion of correct responses is represented in the y axis. **(A)** Stability in performance in the three sessions that preceded each therapy phase (no significant differences observed for either phase). **(B)** Time*Set interaction. **(C)** Time*Stimulation interaction. **(D)** Time*Phase interaction. The *p*-value for each significant interaction is reported above the x axis.

to treatment and show different degrees of generalization. Since differences are expected only in the post-treatment assessment, an interaction was relevant. We also included random intercepts for items, with random slopes for Set, because differences between the treated and the untreated set may vary between items. The model improved significantly with the main effects of Time (pre-, post-treatment), Set (treated, untreated verbs), Phase (1 and 2), Stimulation (Sham, tDCS) and Verb Test (VTinfinitive, VTfinite, VTsentence), and the interactions Time*Set, Time*Phase, Time*Stimulation. **Figures 4**, **5** illustrate the relevant main effects and interactions, and corresponding statistics are reported in **Table 5**. *Post-hoc* pairwise comparisons were computed to characterize the main effect of VerbTest and significant interactions. For this purpose, we used the lsmeans package in R (Lenth and Hervé, 2015), and selected the Scheffe method for adjusting *p*-values for multiple comparisons.

The significant main effect of Time reflected the efficacy of the treatment provided across two phases (ACTION + tDCS or ACTION + Sham), for both treated and untreated verbs. No main effect of Set was observed, as treated and untreated verbs were matched in baseline accuracy. However, the interaction Time*Set was significant (**Figure 4B**), showing greater improvement for treated verbs. *Post-hoc* tests confirm that the lack of differences between verb sets before treatment ($p > 0.9$), but after treatment patients responded more accurately to treated verbs ($z = 4.709$, $p = 0.0001$), and between the two assessments, accuracy improved significantly for both treated ($z = 7.713$, $p < 0.0001$) and untreated verbs ($z = 5.175$,

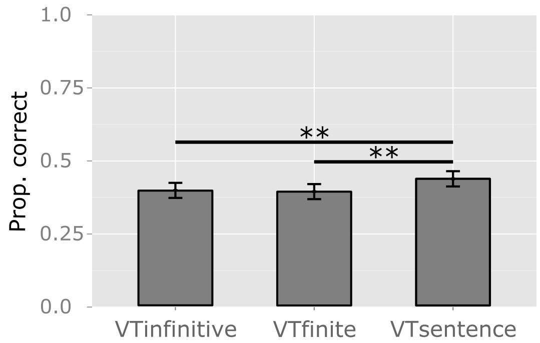


FIGURE 5 | Group results: differences in performance across the three verb tests. The y axis represents the mean proportion of correct responses (Prop. correct). VTinfinitive: sentence completion with a verb in the infinitive. VTfinite: sentence completion with a verb in the correct tense. VTsentence: sentence construction. Significant results are reported: **$p < 0.01$.

TABLE 5 | Summary of fixed effects (verb accuracy).

	Estimate	Std. Error	*z*-Value	Pr(>|z|)
(Intercept)	−1.5163	0.30917	−4.904	9.38E-07***
Time (pre vs. post)	2.58453	0.32153	8.038	9.11E-16***
Set (treated vs. untreated)	−0.0495	0.15385	−0.321	0.74787
Phase (1 vs. 2)	0.97611	0.11365	8.589	<2E-16***
Stimulation (Sham vs. tDCS)	−0.3583	0.11301	−3.17	0.00152**
VerbTest (VTinfinitive vs. VTfinite)	−0.0252	0.091	−0.276	0.78223
(VTinfinitive vs. Vtsentence)	0.23501	0.09038	2.6	0.00932**
Time*Set	−1.6836	0.34451	−4.887	1.02E-06***
Time*Phase	−0.7923	0.152	−5.212	1.86E-07***
Time*Stimulation	0.33311	0.15142	2.2	0.02781*

*Formula: glmer(Accuracy ∼ Time*Set + Time*Phase + Time*Stimulation + VerbTest + (1+Set*Time|Participant) + (1+Set|Item), data, family="binomial").*
*Significant results are reported: ***p < 0.001; **p < 0.01; *p < 0.05.*

$p < 0.0001$). A main effect of stimulation indicates that scores in the tDCS phase were lower than those collected in the Sham phase, and the interaction Time*Stimulation denotes greater improvement in the real tDCS condition. *Post-hoc* tests clarify that improvement was significant both in the Sham ($z = 7.686$, $p < 0.0001$) and tDCS phases ($z = 9.467$, $p < 0.0001$), and while pre-treatment accuracy was lower in the tDCS condition ($z = -3.170$, $p = 0.018$), differences between tDCS and Sham are not significant after treatment ($p > 0.9$) (**Figure 4C**).

Scores observed in Phase 2 were higher than those observed in Phase 1, as shown by the main effect of Phase. The interaction Time*Phase indicates that the amount of improvement was smaller in Phase 2 (**Figure 4D**). In *post-hoc* tests, scores were higher in Phase 2 in comparison to Phase 1 before ($z = 8.589$, $p < 0.0001$) but not after treatment ($z = 1.708$, $p = 0.404$), and significant improvement was observed both in Phase 1 ($z = 10.631$, $p < 0.0001$) and in Phase 2 ($z = 6.448$, $p < 0.0001$). Patients fared better in VTsentence, than in VTinfinitive ($z = 2.600$, $p = 0.034$) and VTfinite ($z = 2.875$, $p = 0.016$), but differences in accuracy between VTinfinitive and VTfinite and the interaction with Time fell short of significance ($p > 0.9$ and $p > 0.4$, respectively) (**Figure 5**).

Control Task: Nonword Repetition

Aspecific improvement was assessed with a nonword repetition task, administered in the three sessions of each assessment phase. Significant changes between assessments 1 and 2, and/or 2 and 3, would indicate aspecific improvement. The null model included random intercepts for Patient and Item. An alternative model introducing random slopes for Time, under the assumption that different patients may present different degrees of aspecific improvement, was the only model that significantly improved fit [$\chi^2(5) = 23.673$, $p = 0.0003$]. This suggests that some participants may show improvement in nonword repetition. Main effects of Assessment phase (1, 2, and 3), Assessment Day (1,2,3, within each phase), and their interaction, did not improve model fit. At the group level, nonword repetition was stable within and between assessments (see **Figure 6**).

Individual Outcomes

Treatment Effects: Lexical Accuracy in Verb Production

For each participant, baseline stability was checked before each treatment phase by comparing lexical accuracy in the three sessions preceding treatment, by means of Cochran's Q-test. All participants presented stable behavior prior to each phase (see **Figure 7**).

Significant improvements between the pre- and post-assessments were computed for each treatment phase, for treated and untreated verbs. Given that each verb had been produced three times in the three sessions of pre- and post-therapy assessments, verb retrieval accuracy scores were calculated by collapsing across performance on the three administrations, thus reaching a final 3-point outcome measure of 3-day lexical accuracy. This procedure has been used to increase score sensitivity (Flöel et al., 2011). Differences between pre- and post-therapy assessments were tested using the Wilcoxon Signed-Rank Test.

Significant improvement of treated verbs was observed in all participants, in both stimulation conditions, except for EC in the real tDCS condition (coinciding with Phase 2) (see **Table 6** and **Figure 8**). The extent of item-specific improvement in each phase was compared using Fisher exact tests. In EC, improvement was significantly greater in the Sham phase, as compared to the tDCS phase (Fisher exact $z = 3.5319$, $p = 0.0002$). Item-specific improvement across phases did not differ significantly in the other participants.

The same procedure was used to assess generalization (improved production of untrained verbs). LF, GC, GD, GP, and EC improved significantly on untreated verbs in the Sham condition (coinciding with Phase 1), but not in the tDCS condition (Phase 2). SP and PG presented significant generalization in the tDCS phase (coinciding with Phase 1), but not in the Sham phase (Phase 2). RL and KC had significant generalization in both phases. The amount of generalization was significantly higher in the tDCS phase for PG (Fisher exact $p < 0.001$) and in the Sham phase for LF (Fisher exact $z =$

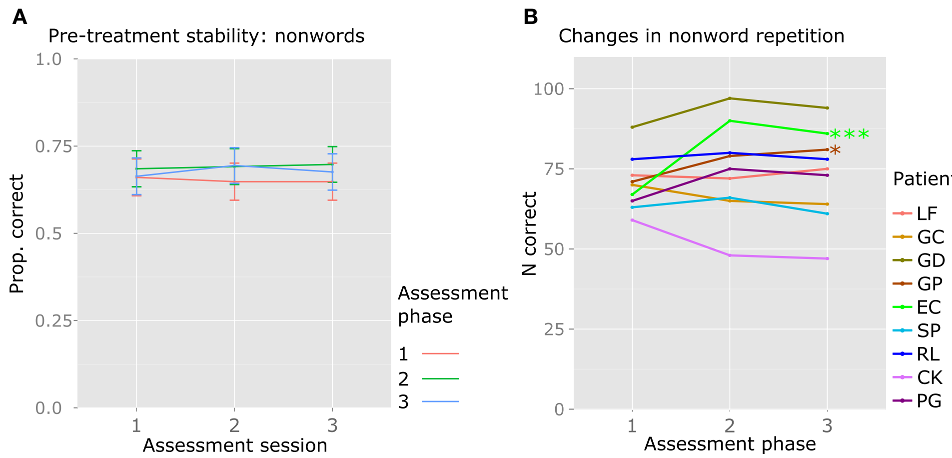


FIGURE 6 | Group and individual results: performance in the control task nonword repetition. (A) Group data; the y axis represents the mean proportion of correct responses (Prop. correct), across the three sessions of each assessment phase, and the lines represent the different assessment phases (before treatment 1, after treatment 1, after treatment 2). **(B)** Individual data; the y axis represents the number of correct responses (N correct) across the three sessions of each assessment phase (max. 108). Significant results are reported: ***$p < 0.001$; *$p < 0.05$. For EC and GP, a significant increase in nonword repetition accuracy was observed between the first and the second assessment phases.

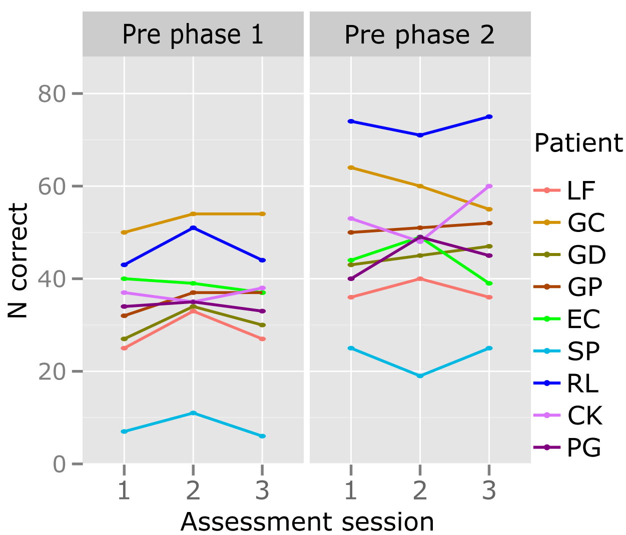


FIGURE 7 | Individual results: behavioral stability prior to each treatment phase. The y axis represents the number of correctly produced verbs (N correct; max. 88 in each of the three sessions that preceded treatment phases 1 and 2). No significant changes are observed.

4.4563, $p = 0.0000$) and GP (Fisher exact $z = 2.1354$, $p = 0.0000$).

Control Task: Nonword Repetition

Nonword repetition scores during the three assessment phases were contrasted, to determine stability prior to each treatment phase. Performance was stable in all participants, except GC, before phase 2 [Cochran's Q-test (2) = 6.222, $p = 0.0446$]. In this subject, nonword accuracy increased significantly between sessions 1 and 2 of the assessment phase that preceded treatment phase 2 [McNemar's χ^2test (2) = 4.1667, $p = 0.0412$], but did not increase further in the third session. We have no clear account for this observation, as session 3 was not significantly different from either session 1 ($p > 0.2$) or session 2 ($p = 0.6$).

Following the procedure used for verbs, the sum total of the correct responses produced during the three sessions of each assessment phase was calculated, to obtain a 3-point measurement of nonword repetition accuracy for each assessment in each participant. The comparison of this measure across assessments 1 (before phase 1), 2 (after phase 1 and before phase 2), and 3 (after phase 2), allowed to measure aspecific improvement in each participant. GP [Friedman's test $\chi^2(2) = 6.889$, $p = 0.0319$] and EC [Friedman's test $\chi^2(2) = 19.4783$, $p < 0.0001$] showed significantly increased accuracy in the second assessment compared to the first, that is, after Sham (treatment phase 1) (GP: Wilcoxon Signed-Rank test = 2.5, $p = 0.0282$; EC: Wilcoxon Signed-Rank test = 0, $p = 0.0007$). Neither patient's accuracy increased further in the third assessment (**Figure 6**).

Discussion

In this study, we found that patients had a stable performance accuracy across the three sessions that preceded each treatment phase. Analyses of pre- and post-treatment data revealed main effects of Time, Phase, Stimulation, and Verb Test. The interactions Time*Phase, Time*Set, and Time*Stimulation were significant. Performance in the control task (nonword repetition) was stable across assessments. Baseline stability and lack of significant changes in a control task allow to attribute the observed changes to therapy (Nickels et al., 2015). Overall, we observe better verb retrieval in sentence construction than in the other two verb tests. In addition, significant improvement is observed for both treated and untreated verbs. The amount of

TABLE 6 | Individual treatment outcomes for treated and untreated verbs.

Participant	ACTION+	Phase	Treated verbs				Untreated Verbs			
			Pre	**Post**	***V***	***p***	**Pre**	**Post**	***V***	***p***
LF	Sham	1	6	28	0.000	0.000	2	12	4.000	0.012
	tDCS	2	9	38	0.000	0.000	11	8	20.000	0.890
GC	Sham	1	13	34	0.000	0.000	15	23	19.500	0.025
	tDCS	2	23	56	0.000	0.000	24	27	27.000	0.307
GD	Sham	1	19	59	0.000	0.000	17	24	8.000	0.040
	tDCS	2	24	59	0.000	0.000	24	27	9.000	0.215
GP	Sham	1	14	46	0.000	0.000	14	21	15.000	0.049
	tDCS	2	23	45	10.000	0.001	21	21	33.000	0.519
EC	Sham	1	11	33	5.000	0.000	11	21	9.000	0.014
	tDCS	2	17	21	32.500	0.168	17	23	16.500	0.060
SP	Sham	2	5	18	0.000	0.006	5	9	4.000	0.205
	tDCS	1	0	25	0.000	0.000	0	6	0.000	0.047
RL	Sham	2	39	57	0.000	0.002	39	46	9.000	0.048
	tDCS	1	20	56	0.000	0.000	21	41	7.000	0.000
CK	Sham	2	25	43	0.000	0.002	23	34	18.000	0.012
	tDCS	1	16	42	0.000	0.000	13	29	9.000	0.005
PG	Sham	2	34	47	5.500	0.003	35	31	42.000	0.811
	tDCS	1	9	42	0.000	0.000	9	16	15.000	0.049

Pre- and Post-scores are expressed by the total number of correct responses in each assessment phase (max = 60). Pre- and post-treatment scores were compared by the Wilcoxon Signed-Rank Test.

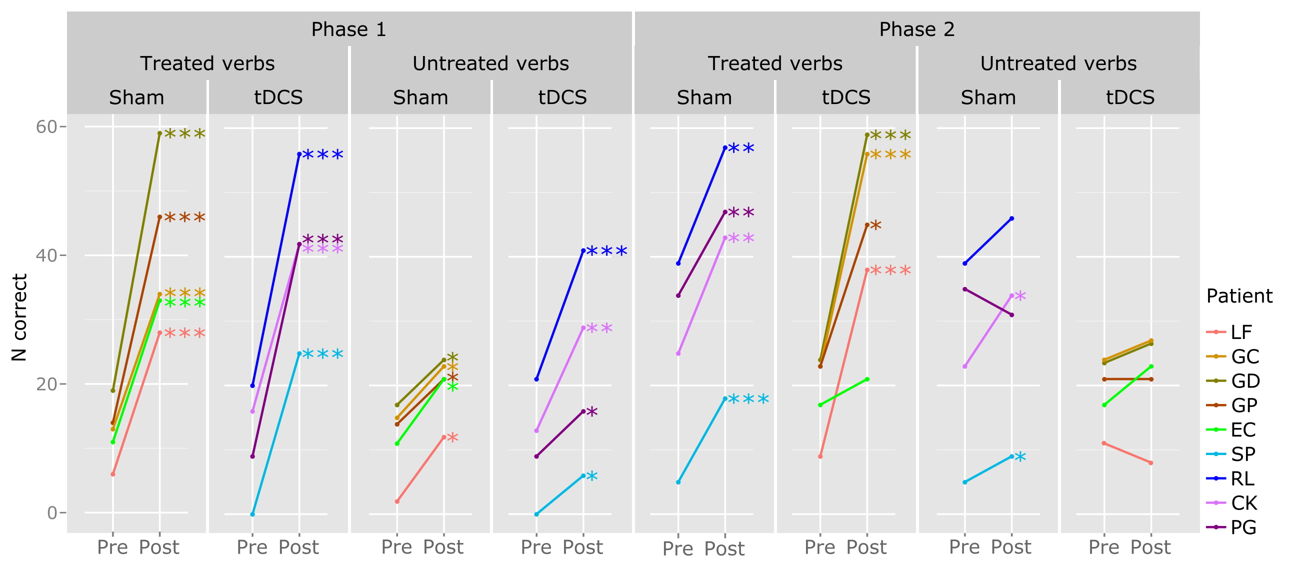


FIGURE 8 | Individual results: effects of treatment in verb retrieval. The y axis represents the number of correct responses (N correct; max. 60, corresponding to 20 verbs over 3 tests). This information is available for treated (left) and untreated verbs (right), for each treatment phase and stimulation condition. Significant results are reported: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

improvement is larger for treated verbs, in Phase 1, and in the real tDCS phase. Individually, all patients showed both item specific improvement and generalization, to different degrees across phases and stimulation conditions. In the following section we discuss the nature of treatment effects and the potential contribution of tDCS to these effects.

Item-specific Effects and Generalization with ACTION

Speech/Language Therapy (ACTION ± tDCS) effectively increased response accuracy, and this improvement was statistically significant for both treated and untreated verbs, at the group level. Albeit present for both sets, improvement was larger for treated verbs. This outcome was expected, as other studies have shown the efficacy of treating verb production in sentences (Edwards and Tucker, 2006), in particular when knowledge of predicate-argument structure is trained explicitly (Fink et al., 1992; Webster et al., 2005; Thompson et al., 2013). Semantic (Edwards and Tucker, 2006), phonemic (e.g., Fink et al., 1992), written word (Conroy et al., 2009), and repetition cues (e.g., Weinrich et al., 1999) all improved retrieval of treated verbs. Indeed, the verbs included in ACTION-based treatment improved in every phase of therapy in all subjects, except for EC, who improved only in Phase 1.

Comparable pre-treatment accuracy across the two sets is essential to identify generalization. Post-treatment accuracy improved significantly for both sets at the group level. In addition, significant generalization occurred in individual cases. It was present in 9/9 participants, either in the first phase (9/9) or in both phases (2/9). ACTION treatment yielded generalization in Dutch and German individuals with aphasia (Bastiaanse et al., 2006; Links et al., 2010). Its Italian adaptation, that adds a specific focus on verb morphology, further encourages the adoption of a structured cueing hierarchy in order to provide patients with a strategy conducive to both item-specific and generalized improvement.

Stable nonword repetition performance at the group level suggests that improvement of verb retrieval was due to treatment, and not to task practice (Nickels et al., 2015). The same holds at the individual level, except in EC and GP, whose nonword repetition accuracy improved in the same phase in which generalization occurred. Prior to participating in this study, EC had not received Speech-Language Therapy for 4 years, and GC had followed (not during his participation in this study) a treatment protocol that also included repetition tasks. For these two cases, improvement in an untreated task does not allow to establish the reasons for better performance on untrained verbs in experimental tasks—it could be attributed to treatment, but also to a charm effect or to the adoption of strategies external to ACTION. Nevertheless, since in both subjects performance in additional tasks (e.g., object naming) was stable throughout the protocol, and since in the other participants nonword repetition did not improve, it is reasonable to attribute generalization to ACTION, at least in part, also in the case of EC and GP.

Which mechanisms may have resulted on generalization? The representation of a verb specifies, in addition to suprasegmental and syllabic/segmental features (represented also for nouns), lexical-grammatical properties that are exclusive to verbs, such as conjugation, inflectional paradigm, transitivity, predicate-argument structure, etc.). Such properties are verb-specific, but are similar for large sets of items. In fact, there is evidence that different verbs share information about the syntactic structures in which they occur (Pickering and Branigan, 1998), and that this can result in structural priming between sentences that include different verbs (Bock, 1986). Consequently, training predicate-argument structure production in the context of a specific verb can facilitate retrieval of the same predicate-argument structure for another verb. And in turn, it can facilitate activation of lexical items that are semantically appropriate to the active predicate-argument structure (Bock, 1986). This lexical selection bias can enhance access to the representations of untreated verbs. In short, participants might have benefited from improved retrieval of treated verbs, and from recovered knowledge of typical argument structure to cue the retrieval of untreated verbs. At the end of the treatment protocol, this might have yielded both item-specific recovery and generalization.

Interestingly, generalization was observed in protocols that require production of verbs in sentence context (Bastiaanse et al., 2006; Links et al., 2010; Thompson et al., 2013), but not in protocols focusing on verb production at the single-word level, even when action naming was preceded by explicit discussion of that verb's argument structure (e.g., with modified semantic feature analysis for verbs; Wambaugh and Ferguson, 2007). This suggests that generalization depends not only on training lexical verb retrieval or on recovering abstract knowledge of argument structure, but also on actually producing predicate argument structures.

The role of structural complexity should also be considered here. In the second week of each therapy phase, the treatment task reached a higher level of complexity than that used in any of the tasks used during assessment. At this stage, participants were prompted with an image and an adverb and were asked to produce full sentences with verbs inflected in the correct tense. Even the most demanding task used to measure improvement (sentence construction) was simpler than this treatment task in some respects, as participants need not inflect the verb in one of three tenses. Importantly, all tasks tackled related linguistic operations. The Complexity Account for Treatment Efficacy predicts improvement in linguistically related, less complex tasks (Thompson et al., 2003). Improved verb retrieval for untreated verbs in less complex, related structures, was also reported (Thompson et al., 2013), with 3-argument verb treatment resulting in improved production of 1- and 2-argument verbs in sentences. In addition, morphosyntactic complexity was shown to have an impact in verb retrieval, with aphasic patients displaying poorer retrieval of finite than nonfinite verbs (Bastiaanse, 2011). By treating the production of tense morphology (a knowledge that can be generalized), we may have decreased task complexity for both treated and untreated verbs, thereby allowing resource allocation for lexical selection processes.

In most participants, difficulties in sentence construction were associated with damage to multiple levels of language processing, including semantics, lexical retrieval, sublexical conversion procedures, working memory and grammar (thematic role assignment, realization of predicate-argument structure, and morphosyntactic processes). Focusing treatment on verb retrieval, verbal morphology and predicate-argument structure in sentence-level tasks may have indirectly yielded additional benefits (generalization) by alleviating associated impairments and/or implicitly teaching participants how to circumvent them. For example, training may have increased working memory capacity, and the improvement of grammatical processing may have decreased the cognitive load associated with sentence construction, resulting in more efficient allocation of resources to lexical retrieval.

Given that verb accuracy was calculated by collapsing accuracy across three different tasks, we also considered whether this scoring procedure influenced the evaluation of performance and the resulting patterns of improvement. There was a main effect of Verb Test, indicating that participants retrieved verbs more accurately in the VTsentence (sentence construction) than in the other two tasks, possibly because in this task patients read cues about the nature of the constituents to produce (see **Figure 2**), and this may have facilitated access to predicate-argument structure. Patient also had more time to respond in this task (30 s, in comparison to 20 s in the other tasks), to account for the higher number of words that needed to be produced. Importantly, after therapy, lexical verb retrieval improved in all tests (VTinfinitive, VTfinite, VTsentence), without significant across-task differences.

Since participants were treated in two phases, and were randomly assigned to the two stimulation sequences (tDCS, then sham vs. sham, then tDCS), the effect of timing on treatment is worth considering. Participants improved more in Phase 1 than in Phase 2. This may have occurred because there was more room for improvement in Phase 1 (subjects had not received any treatment for several months), and recovery plateaued by the end of Phase 2. Following TUF-based treatment (Thompson and Shapiro, 2005), Dickey and Yoo (2013) showed that improvement of treated and untreated verbs depends on different dose-response relations. Treated verbs were acquired faster and linearly, whereas generalization emerged more slowly, its learning curve accelerating over time. In the present study, both item-specific improvement and generalization were larger in Phase 1, and the pattern for untreated verbs was opposite to that reported by Dickey and Yoo (2013).

tDCS

Scores before and after the tDCS treatment phase were lower than those before and after the Sham phase, as shown by the main effect of Stimulation. In fact, we successfully controlled pre-treatment accuracy across treated and untreated verbs in each phase, but accuracy across phases was more difficult to balance, as it depended on the extent to which each participant improved in Phase 1. The Time*Stimulation interaction suggests that, in spite of lower initial scores, improvement was greater in the tDCS phase. However, this result must be taken cautiously, as the steeper slope for real tDCS may reflect a true enhancement due to successful neuromodulation, but also a ceiling effect for the Sham condition. In other words, if participants could not improve further than observed, the slope may be steeper in the tDCS condition just because participants started off with lower accuracy. We discuss these possibilities (a true stimulation effect and a ceiling effect) in the next paragraphs.

To our knowledge, this is the first time that tDCS is applied together with a treatment program that targets verb production in sentence context and includes explicit morphosyntactic training. Neuroimaging studies suggest that sentence production and verb inflection require computations that are widely distributed in the brain (e.g., Perani et al., 1999; Thompson et al., 2007). Given that tDCS is more effective when the electrodes are placed directly above areas involved in the cognitive processes associated with stimulation (Marangolo et al., 2013a), it is possible that tDCS is more effective when associated with cognitive functions that have a more circumscribed representation. Thus, ACTION could be considered a less optimal protocol to pair with tDCS. Nevertheless, previous research contradicts the idea that widespread representation of the cognitive processes engaged by a task may decrease efficacy of neuromodulation. For example, benefits from tDCS were reported in association with conversational therapy (Marangolo et al., 2013b).

Stimulation was delivered to different sites in different participants. We did this to ensure that tDCS was applied over healthy tissue in each case. In previous research (Baker et al., 2010), stimulation sites were identified based on each individual's fMRI activation during correct naming. This procedure was selected to ensure that the stimulated area was involved in the to-be-treated task, and to putatively allow tDCS to enhance patterns of activation known to correlate with good performance. While this approach has pragmatic limitations (discussed in de Aguiar et al., 2015), it is indeed relevant to target areas for stimulation that have at least the potential to be involved in the task. Our decision in terms of stimulation site may have resulted in a more efficient pairing of functional role of the area and treatment task in some cases than in others (see Marangolo et al., 2013a), but this approach was preferred to stimulation of lesioned tissue. First, because lesioned tissue can disturb current flow (Datta et al., 2011) and, most importantly, because recovery is typically associated with activation of peri-lesional or contra-lesional areas (Schlaug et al., 2008) and tDCS directly over lesioned areas was reported to be ineffective (Hesse et al., 2007).

Individual data analyses highlight another important issue. For treated verbs, EC had larger improvement in the Sham condition. For untreated verbs, improvement was greater after tDCS for PG, and after Sham for LF and PG. Crucially, these participants showed greater improvement in Phase 1 than in Phase 2, regardless of stimulation condition. The same was true at the group level. Therefore, it is not clear whether across-phase differences are due to type of stimulation (tDCS vs. Sham) or to treatment phase (1 vs. 2). In cross-over designs, in which typically two treatments are administered over two phases, treatment order can massively influence outcome. In our sample, five participants received Sham first and four received tDCS first. With an uneven number of subjects, and a significantly larger improvement in Phase 1, the design is somewhat biased toward larger improvements in the Sham condition. Nonetheless, group analyses show greater improvement in the tDCS phase, for both treated and untreated verbs.

All things considered, in the same way that we cannot rule out a ceiling effect for Sham, we can also not exclude the possibility that data reflect a true, tDCS-related enhancement. Assuming a real effect of tDCS, our data is in line with previous research. Performance in tasks using verbs, such as action naming (Marangolo et al., 2013a) and spontaneous speech (Marangolo et al., 2013b, 2014), showed significant therapy enhancement after stimulation of Broca's area. In our study, the anode was placed over Broca's area in three participants and over the neighboring left hemisphere cortex in five. Considering that we focused on verb retrieval accuracy, our data are consistent with those of Marangolo et al. (2013a), showing that stimulation of Broca's area (and of the surrounding cortex)[6] can enhance verb production. Since a bi-cephalic montage was used in all participants, the observed effects could be due to a combination of the excitation induced by the anode placed over LH perilesional areas, and of the active role of the cathode over contralesional areas (Nitsche et al., 2008), which may have contributed to balancing interhemispheric competition (Murase et al., 2004).

In addition, lack of a three-way interaction involving Set (Time*Stimulation*Set) suggests that greater improvement in the tDCS phase involves both treated and untreated verbs. Moreover, control for aspecific improvement in verb production was achieved (pre-treatment performance was stable, and no group-level effects were observed for nonwords), and therefore data indicate that improvement of untreated items reflects generalization. Of the five participants who received Sham first, all showed generalization in Phase 1 and none in Phase 2. Of the four participants who received tDCS first, all generalized in Phase 1, but two also generalized in Phase 2 (when they received Sham). This could either mean that Sham increased generalization in both phases, or that administering tDCS in the first phase extended the generalization potential to the subsequent Sham phase. This latter possibility receives some support from group data, through the observation of larger item-specific improvement and generalization in the tDCS phase. Nevertheless, we reiterate that the results regarding tDCS are not conclusive, as it is not possible to distinguish between a real tDCS-induced modulation and a ceiling effect in the Sham condition. Furthermore, it should be highlighted that we report data from a relatively small sample. Considering the fact that response to tDCS is characterized by a large inter-subject variability (Horvath et al., 2014), replication with a larger sample is essential to support the findings reported in the current study.

[6]This was the stimulation target for 8/9 patients.

Conclusion

The ACTION protocol improved lexical retrieval for both treated and untreated verbs. With generalization considered as the ultimate goal of aphasia therapy (Dickey and Yoo, 2013), results highlight the importance of engaging explicit morphosyntactic knowledge during rehabilitation of verb retrieval. Item-specific improvement was considerably larger than improvement of untreated items, but all participants improved significantly on both sets of verbs. Improvement was more marked in the first phase of treatment. Even though this study was not designed to assess the timing constraints of therapy, results stress the need to investigate the time-course of both item-specific and generalized improvement. The effects of bi-cephalic tDCS administered concurrently with ACTION are to be interpreted carefully, but while a ceiling effect cannot be excluded, larger therapy effects were observed during tDCS than Sham, for treated and untreated verbs.

Acknowledgments

This publication is supported by COST (European Cooperation in Science and Technology). Funding was provided by PAT (Provincia Autonoma di Trento) and Fondazione CaRiTRO (Cassa di Risparmio di Trento e Rovereto) to GM, and by Erasmus Mundus Joint Doctorate (EMJD) program IDEALAB (International Doctorate in Experimental Approaches to Language And Brain; Macquarie University, Newcastle University, University of Groningen, University of Trento and University of Potsdam) to VD (FPA 2012-0025; cohort 2012-1713). We thank Alberto Morandi, Francesca Odorizzi, Elena Facci, Eloisa Iellici, Silvia Di Stefano, Katharina Nimz, and Adrià Rofes for their help in different stages of this project. The illustrations of ACTION were made by Victor Xandri Antolín.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnbeh.2015.00190

References

Baker, J. M., Rorden, C., and Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke* 41, 1229–1236. doi: 10.1161/STROKEAHA.109.576785

Bastiaanse, R. (2011). The retrieval and inflection of verbs in the spontaneous speech of fluent aphasic speakers. *J. Neurolinguistics* 24, 163–172. doi: 10.1016/j.jneuroling.2010.02.006

Bastiaanse, R., Hurkmans, J., and Links, P. (2006). The training of verb production in Broca's aphasia: a multiple-baseline across-behaviours study. *Aphasiology* 20, 298–311. doi: 10.1080/02687030500474922

Bastiaanse, R., Jonkers, R., Quak, C.h., and Varela Put, M. (1997). *Werkwoordproductie op Woord en Zinsniveau [Verb Production at the Word and Sentence Level]*. Lisse: Swets Test Publishers.

Bates, D., Maechler, M., Bolker, B., and Walker, S. (2014). *_lme4: Linear Mixed-effects Models Using Eigen and S4_*. R Package version 1.1-7. Available online at: http://CRAN.R-project.org/package=lme4

Bock, J. K. (1986). Meaning, sound, and syntax: lexical priming in sentence production. *J. Exp. Psychol. Learn. Mem. Cogni.* 12, 575. doi: 10.1037/0278-7393.12.4.575

Boyle, M., and Coelho, C. A. (1995). Application of semantic feature analysis as a treatment for aphasic dysnomia. *Am. J. Speech Lang. Pathol.* 4, 94–98. doi: 10.1044/1058-0360.0404.94

Brady, M. C., Kelly, H., Godwin, J., and Enderby, P. (2012). Speech and language therapy for aphasia following stroke. *Cochrane Database Syst. Rev.* 5, 420–425. doi: 10.1002/14651858.CD000425.pub2

Caramazza, A., and Hillis, A. E. (1991). Lexical organization of nouns and verbs in the brain. *Nature* 349, 788–790. doi: 10.1038/349788a0

Conroy, P., Sage, K., and Lambon Ralph, M. A. (2009). The effects of decreasing and increasing cue therapy on improving naming speed and accuracy for verbs and nouns in aphasia. *Aphasiology* 23, 707–730. doi: 10.1080/02687030802165574

Dal Pan, G., Stern, Y., Sano, M., and Mayeux, R. (1989). Clockdrawing in neurological disorders. *Behav. Neurol.* 2, 39–48. doi: 10.1155/1989/470135

DaSilva, A. F., Volz, M. S., Bikson, M., and Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *J. Vis. Exp: JoVE*, 2011:2744. doi: 10.3791/2744

Datta, A., Baker, J. M., Bikson, M., and Fridriksson, J. (2011). Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimul.* 4, 169–174. doi: 10.1016/j.brs.2010.11.001

de Aguiar, V., Paolazzi, C. L., and Miceli, G. (2015). tDCS in post-stroke aphasia: the role of stimulation parameters, behavioral treatment and patient characteristics. *Cortex* 63, 296–316. doi: 10.1016/j.cortex.2014.08.015

de Diego Balaguer, R., Rodríguez-Fornells, A., Rotte, M., Bahlmann, J., Heinze, H. J., and Münte, T. F. (2006). Neural circuits subserving the retrieval of stems and grammatical features in regular and irregular verbs. *Hum. Brain Mapp.* 27, 874–888. doi: 10.1002/hbm.20228

Den Ouden, D. B., Fix, S., Parrish, T. B., and Thompson, C. K. (2009). Argument structure effects in action verb naming in static and dynamic conditions. *J. Neurolinguistics* 22, 196–215. doi: 10.1016/j.jneuroling.2008.10.004

Dickey, M. W., and Yoo, H. (2013). Acquisition versus generalization in sentence production treatment in aphasia: dose-response relationships. *Procedia* 94, 281–282. doi: 10.1016/j.sbspro.2013.09.141

Edwards, S., and Tucker, K. (2006). Verb retrieval in fluent aphasia: A clinical study. *Aphasiology*, 20, 644–675. doi: 10.1080/02687030600631827

Fertonani, A., Rosini, S., Cotelli, M., Rossini, P. M., and Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behav. Brain Res.* 208, 311–318. doi: 10.1016/j.bbr.2009.10.030

Fink, R. B., Martin, N., Schwartz, M. F., Saffran, E. M., and Myers, J. L. (1992). Facilitation of verb retrieval skills in aphasia: a comparison of two approaches. *Clin. Aphasiol.* 21, 263–275.

Flöel, A., Meinzer, M., Kirstein, R., Nijhof, S., Deppe, M., Knecht, S., et al. (2011). Short-term anomia training and electrical brain stimulation. *Stroke* 42, 2065–2067.

Friederici, A. D., Hahne, A., and Von Cramon, D. Y. (1998). First-pass versus second-pass parsing processes in a Wernicke's and a Broca's aphasic: electrophysiological evidence for a double dissociation. *Brain Lang.* 62, 311–341. doi: 10.1006/brln.1997.1906

Gandiga, P. C., Hummel, F. C., and Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin. Neurophysiol.* 117, 845–850. doi: 10.1016/j.clinph.2005.12.003

Garrett, M. F. (1980). "Levels of processing in sentence production," in *Language Production.* Vol. 1*: Speech and Talk*, ed B. Butterworth (London: Academic Press), 176–220.

Hamilton, R. H., Chrysikou, E. G., and Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain Lang.* 118, 40–50. doi: 10.1016/j.bandl.2011.02.005

Hesse, S., Werner, C., Schonhardt, E. M., Bardeleben, A., Jenrich, W., and Kirker, S. G. B. (2007). Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. *Restor. Neurol. Neurosci.* 25, 9–16. Retrieved from: http://www.ebstech.de/publications/motor_function_domain/Hesse_Restor_Neurol_Neurosci_2007.pdf

Horvath, J. C., Carter, O., and Forte, J. D. (2014). Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). *Front. Syst. Neurosci.* 8:2. doi: 10.3389/fnsys.2014.00002

Howard, D., Best, W., and Nickels, L. (2015). Optimising the design of intervention studies: critiques and ways forward. *Aphasiology* 29, 1–37. doi: 10.1080/02687038.2014.985884

Jaeger, T. F. (2008). Categorical data analysis: Away from ANOVAs (transformation or not) and towards logit mixed models. *J. Mem. Lang.* 59, 434–446. doi: 10.1016/j.jml.2007.11.007

Kielar, A., Milman, L., Bonakdarpour, B., and Thompson, C. K. (2011). Neural correlates of covert and overt production of tense and agreement morphology: evidence from fMRI. *J. Neurolinguistics* 24, 183–201. doi: 10.1016/j.jneuroling.2010.02.008

Laska, A. C., Hellblom, A., Murray, V., Kahan, T., and Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *J. Intern. Med.* 249, 413–422. doi: 10.1046/j.1365-2796.2001.00812.x

Lenth, R. V., and Hervé, M. (2015). *lsmeans: Least-Squares Means*. R package version 2.17. Available online at: http://CRAN.R-project.org/package=lsmeans

Links, P., Hurkmans, J., and Bastiaanse, R. (2010). Training verb and sentence production in agrammatic Broca's aphasia. *Aphasiology* 24, 1303–1325. doi: 10.1080/02687030903437666

Liuzzi, G., Freundlieb, N., Ridder, V., Hoppe, J., Heise, K., Zimerman, M., et al. (2010). The involvement of the left motor cortex in learning of a novel action word lexicon. *Curr. Biol.* 20, 1745–1751. doi: 10.1016/j.cub.2010.08.034

Marangolo, P., Fiori, V., Calpagnano, M. A., Campana, S., Razzano, C., Caltagirone, C., et al. (2013b). tDCS over the left inferior frontal cortex improves speech production in aphasia. *Front. Hum. Neurosci.* 7:539. doi: 10.3389/fnhum.2013.00539

Marangolo, P., Fiori, V., Campana, S., Calpagnano, M. A., Razzano, C., Caltagirone, C., et al. (2014). Something to talk about: enhancement of linguistic cohesion through tdCS in chronic non fluent aphasia. *Neuropsychologia* 53, 246–256. doi: 10.1016/j.neuropsychologia.2013.12.003

Marangolo, P., Fiori, V., Di Paola, M., Cipollari, S., Razzano, C., Oliveri, M., et al. (2013a). Differential involvement of the left frontal and temporal regions in verb naming: a tDCS treatment study. *Restor. Neurol. Neurosci.* 31, 63–72. doi: 10.3233/RNN-120268

Meinzer, M., Jähnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., et al. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex* 50, 137–147. doi: 10.1016/j.cortex.2013.07.013

Miceli, G., Amitrano, A., Capasso, R., and Caramazza, A. (1996). The treatment of anomia resulting from output lexical damage: analysis of two cases. *Brain Lang.* 52, 150–174. doi: 10.1006/brln.1996.0008

Miceli, G., Laudanna, A., and Capasso, R. (2006). *Batteria Per L'analisi Dei Deficit Afasici: BADA*. Bologna: EMS.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., et al. (2008). Improved naming after transcranial direct current stimulation in aphasia. *J. Neurol. Neurosurg. Psychiatr.* 79:451e453. doi: 10.1136/jnnp.2007.135277

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., et al. (2013). Transcranial direct current stimulation (tDCS) and language. *J. Neurol. Neurosurg. Psychiatry* 84, 832–842. doi: 10.1136/jnnp-2012-302825

Murase, N., Duque, J., Mazzocchio, R., and Cohen, L. (2004). Influence of interhemispheric interactions on motor function in chronic stroke. *Ann. Neurol.* 55, 400–409. doi: 10.1002/ana.10848

Nickels, L., Best, W., and Howard, D. (2015). Optimising the ingredients for evaluation of the effects of intervention. *Aphasiology* 29, 1–25. doi: 10.1080/02687038.2014.1000613

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* 1, 206–223. doi: 10.1016/j.brs.2008.06.004

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., et al. (2004). Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. *Neuroimage* 21, 99–111. doi: 10.1016/j.neuroimage.2003.08.026

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., and Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital. J. Neurol. Sci.* 8, 537–548. doi: 10.1007/BF02333660

Perani, D., Cappa, S. F., Schnur, T., Tettamanti, M., Collina, S., Rosa, M. M., et al. (1999). The neural correlates of verb and noun processing: a PET study. *Brain* 122, 2337–2344. doi: 10.1093/brain/122.12.2337

Pickering, M. J., and Branigan, H. P. (1998). The representation of verbs: evidence from syntactic priming in language production. *J. Mem. Lang.* 39, 633–651. doi: 10.1006/jmla.1998.2592

Rofes, A., de Aguiar, V., and Miceli, G. (2015). A minimal standardization setting for language mapping tests: an Italian example. *Neurol. Sci.* 36, 1113–1119. doi: 10.1007/s10072-015-2192-3

Rose, M., and Sussmilch, G. (2008). The effects of semantic and gesture treatments on verb retrieval and verb use in aphasia. *Aphasiology* 22, 691–706. doi: 10.1080/02687030701800800

Saffran, E., Schwartz, M., and Marin, O. (1980). "Evidence from aphasia: Isolating the components of a production model," in *Language Production*, Vol. 1, Speech and Talk, ed B. Butterworth (London: Academic Press), 221–241.

Schlaug, G., Renga, V., and Nair, D. (2008). Transcranial direct current stimulation in stroke recovery. *Arch. Neurol.* 65, 1571–1576. doi: 10.1001/archneur.65.12.1571

Schwartz, M. F. (2013). "Patterns of speech production deficit within and across aphasia syndromes: application of a psycholinguistic model," in *The Cognitive Neuropsychology of Language*, eds M. Coltheart, G. Sartori, and R. Jobb (East Sussex: Psychology Press), 163–199.

Shetreet, E., Palti, D., Friedmann, N., and Hadar, U. (2007). Cortical representation of verb processing in sentence comprehension: number of complements, subcategorization, and thematic frames. *Cereb. Cortex* 17, 1958–1969. doi: 10.1093/cercor/bhl105

Spinnler, H. and Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 8, 1–120.

Thompson, C., and Shapiro, L. (2005). Treating agrammatic aphasia within a linguistic framework: treatment of Underlying Forms. *Aphasiology* 19, 1021–1036. doi: 10.1080/02687030544000227

Thompson, C. K., Bonakdarpour, B., Fix, S. C., Blumenfeld, H. K., Parrish, T. B., Gitelman, D. R., et al. (2007). Neural correlates of verb argument structure processing. *J. Cogn. Neurosci.* 19, 1753–1767. doi: 10.1162/jocn.2007.19.11.1753

Thompson, C. K., Riley, E. A., Den Ouden, D. B., Meltzer-Asscher, A., and Lukic, S. (2013). Training verb argument structure production in agrammatic aphasia: behavioral and neural recovery patterns. *Cortex* 49, 2358–2376. doi: 10.1016/j.cortex.2013.02.003

Thompson, C. K., Shapiro, L. P., Kiran, S., and Sobecks, J. (2003). The role of syntactic complexity in treatment of sentence deficits in agrammatic aphasia: the complexity account of treatment efficacy (CATE). *J. Speech Lang. Hear. Res.* 46, 591–607. doi: 10.1044/1092-4388(2003/047)

Thompson, C. K., Shapiro, L. P., Tait, M. E., Jacobs, B. J., and Schneider, S. L. (1996). Training wh-question production in agrammatic aphasia: analysis of argument and adjunct movement. *Brain Lang.* 52, 175–228. doi: 10.1006/brln.1996.0009

Tranel, D., Martin, C., Damasio, H., Grabowski, T. J., and Hichwa, R. (2005). Effects of noun–verb homonymy on the neural correlates of naming concrete entities and actions. *Brain Lang.* 92, 288–299. doi: 10.1016/j.bandl.2004.01.011

Tyler, L. K., Stamatakis, E. A., Post, B., Randall, B., and Marslen-Wilson, W. (2005). Temporal and frontal systems in speech comprehension: an fMRI study of past tense processing. *Neuropsychologia* 43, 1963–1974. doi: 10.1016/j.neuropsychologia.2005.03.008

Vines, B. W., Norton, A. C., and Schlaug, G. (2011). Non-invasive brain stimulation enhances the effects of melodic intonation therapy. *Front. Psychol.* 2:230. doi: 10.3389/fpsyg.2011.00230

Wambaugh, J. L., and Ferguson, M. (2007). Application of semantic feature analysis to retrieval of action names in aphasia. *J. Rehabil. Res. Dev.* 44, 381. doi: 10.1682/JRRD.2006.05.0038

Wambaugh, J. L., Mauszycki, S., and Wright, S. (2014). Semantic feature analysis: application to confrontation naming of actions in aphasia. *Aphasiology* 28, 1–24. doi: 10.1080/02687038.2013.845739

Webster, J., Morris, J., and Franklin, S. (2005). Effects of therapy targeted at verb retrieval and the realisation of the predicate argument structure: a case study. *Aphasiology* 19, 748–764. doi: 10.1080/026870305001 66957

Webster, J., and Whitworth, A. (2012). Treating verbs in aphasia: exploring the impact of therapy at the single word and sentence levels. *Int. J. Lang. Commun. Disord.* 47, 619–636. doi: 10.1111/j.1460-6984.2012.00174.x

Weinrich, M., Boser, K. I., and McCall, D. (1999). Representation of linguistic rules in the brain: evidence from training an aphasic patient to produce past tense verb morphology. *Brain Lang.* 70, 144–158. doi: 10.1006/brln.1999.2141

Weinrich, M., Shelton, J. R., Cox, D. M., and McCall, D. (1997). Remediating production of tense morphology improves verb retrieval in chronic aphasia. *Brain Lang.* 58, 23–45. doi: 10.1006/brln.1997.1757

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

PERSPECTIVE
published: 21 August 2015
doi: 10.3389/fnbeh.2015.00222

Translating novel findings of perceptual-motor codes into the neuro-rehabilitation of movement disorders

Mariella Pazzaglia [1,2]* *and Giulia Galli* [2]

[1] Dipartimento di Psicologia, Università degli Studi di Roma "La Sapienza", Rome, Italy, [2] IRCCS Santa Lucia Foundation, Rome, Italy

The bidirectional flow of perceptual and motor information has recently proven useful as rehabilitative tool for re-building motor memories. We analyzed how the visual-motor approach has been successfully applied in neurorehabilitation, leading to surprisingly rapid and effective improvements in action execution. We proposed that the contribution of multiple sensory channels during treatment enables individuals to predict and optimize motor behavior, having a greater effect than visual input alone. We explored how the state-of-the-art neuroscience techniques show direct evidence that employment of visual-motor approach leads to increased motor cortex excitability and synaptic and cortical map plasticity. This super-additive response to multimodal stimulation may maximize neural plasticity, potentiating the effect of conventional treatment, and will be a valuable approach when it comes to advances in innovative methodologies.

Keywords: action observation, plasticity, rehabilitation, brain stimulation, motor cortex, multisensory rehabilitation

Edited by:
Katiuscia Sacco,
University of Turin, Italy

Reviewed by:
Karen Zentgraf,
University of Münster, Germany
Panthea Heydari,
University of Southern California, USA

****Correspondence:***
Mariella Pazzaglia,
Dipartimento di Psicologia, Università degli Studi di Roma "La Sapienza", Via dei Marsi 78, 00185 Rome, Italy
mariella.pazzaglia@uniroma1.it

Received: *09 May 2015*
Accepted: *07 August 2015*
Published: *21 August 2015*

Citation:
Pazzaglia M and Galli G (2015) Translating novel findings of perceptual-motor codes into the neuro-rehabilitation of movement disorders. Front. Behav. Neurosci. 9:222. doi: 10.3389/fnbeh.2015.00222

Introduction

The inextricable link between action perception and execution was first posited by ideomotor theory and neurophysiological studies on mirror neurons (Prinz, 1990; di Pellegrino et al., 1992; Hommel, 1996). Within the past few years, it has been accepted that the bidirectional flow of perceptual and motor information can be useful in neurorehabilitation (Franceschini et al., 2012; Kantak and Winstein, 2012; Buccino, 2014). More specifically, theory-based evidence (Pomeroy et al., 2005; Garrison et al., 2010) has suggested that combined perceptual-motor training is beneficial in recovering and restoring motor ability after stroke (Small et al., 2012, 2013). Recently, this approach has been successfully applied to a considerable number of experimental lines of research validating how action observation is an effective way to enhance the performance of a specific motor skill (for a review, see Buccino, 2014).

Action Observation Treatment

Observation/Motor Training

During the rehabilitation protocol, patients are typically required to observe a specific movement that is presented in a video clip or demonstrated by an examiner, and contemporaneously (or thereafter) execute what they observe. A match or mismatch between visual signals and one's own motor output re-informs the brain about how the limbs or mouth, for example, should move in order to successfully execute a gesture when a motor command is sent. Accurately reproducing spatial (Heyes and Foster, 2002), temporal (Badets et al., 2006a,b), and inter-limb coordination (Buchanan and Dean, 2010) characterizes movements, facilitates the generation of errorless motor patterns, and/or stimulates online correction output (Hecht et al., 2001; Heyes and Foster, 2002; Casile and Giese, 2006).

Behavioral and neurophysiological studies using combined visual-motor programs have suggested that the observation of a movement can improve motor performance in patients who have suffered a chronic ischemic stroke (Ertelt et al., 2007, 2012; Franceschini et al., 2010, 2012; Ertelt and Binkofski, 2012; Sale and Franceschini, 2012; Bang et al., 2013; Bonifazi et al., 2013; Brunner et al., 2014; Kim et al., 2014b; Marangon et al., 2014; Park et al., 2014a; Sale et al., 2014), patients with Parkinson's disease (PD; Pelosin et al., 2010, 2013; Buccino et al., 2011; Esculier et al., 2014), and in children with cerebral palsy (Sgandurra et al., 2011, 2013; Buccino et al., 2012; Kim and Lee, 2013; Kim et al., 2014a). In the absence of brain injury, this type of treatment can be easily used to benefit patients with poor motor function or decline due to aging (Celnik et al., 2006; Bellelli et al., 2010; Park et al., 2014a). For example, bidirectional perceptual/motor training can be effective in patients with musculoskeletal injuries, such as those undergoing orthopedic surgery for the hip or knee (Bellelli et al., 2010; Park et al., 2014a,b), or in elderly individuals with reduced cognitive ability (Celnik et al., 2006; for a summary of these studies please see **Table 1**).

Even in the brain of motor skill experts such as athletes or musicians, simultaneous training on the execution of a motor act during observation of an action results in better motor outcome (Haslinger et al., 2005; Mann et al., 2010).

Positive Impact of Action Observation/Execution Treatment

Rehabilitative treatments based on perceptual-motor codes produce more effective results than motor acts that are mentally simulated (Gatti et al., 2013), motor training alone, or action observation alone (Hecht et al., 2001; Casile and Giese, 2006). Further, this rehabilitative approach seems to work quicker, and is more effective and more stable over long duration (Ertelt et al., 2007). One of the most striking advantages of this treatment is that it does not target one specific region of the body. In other words, this approach can be used to guide any biological effector (mouth, upper limbs, lower limbs, and trunk) in the production of an action.

During early stages of illness, motor observation and imagery could prevent the cortico-motor depression that is caused by limited use of the limbs (Bassolino et al., 2014). In the sub-acute phase, these two factors could stimulate and enhance the beneficial effects of motor training (Sale et al., 2014).

Several studies have recently reported the positive effects of motor imagery training on balance and gait performance (Dunsky et al., 2008), as well as on upper-limb function (Page et al., 2001), in patients with chronic stroke (Ietswaart et al., 2011) and on lower-limb function following spinal cord injury (Hotz-Boendermaker et al., 2011). Thus, it has been suggested that action observation could be a complementary training to facilitate the effect of an imagined motor task.

However, as observation of a movement provides unequivocal visual stimuli to the observer, it facilitates actual motor output more than imagining motions *per se*. The precise execution dynamic of an observed motor act could inform the motor imagery to improve the training supporting the kinesthetic aspects of the action, both when the classic motor training is not yet possible and after during the combined perceptual-motor rehabilitation treatments.

Despite the fact that training is enhanced when it is simultaneously combined with both action observation and execution (Stefan et al., 2005; Celnik et al., 2006, 2008), or when observation follows physical practice during early consolidation, some issues remain and further improvements can be made. For example, the time course of motor consolidation should be investigated in order to determine if it occurs flexibly across multiple timescales. Moreover, it is unclear whether action observation training is effective due to the recall of physical practice or motor performance *per se*, or because motor memories are relearned.

Towards Multimodal Prediction in Rehabilitation

The Effect of Multimodal Experience on Perceptual-Motor Codes

It is clear that the motor memory of an action is a multimodal experience that is modulated by visual (Haslinger et al., 2005), auditory (Kaplan and Iacoboni, 2007), and even olfactory (Pazzaglia, 2015) input. Given the mechanism that unifies action perception and action execution, it is highly plausible that, in rehabilitation, the consolidation of an early motor memory or recollection of a motor gesture may benefit from the use of different perceptual cues during the practice of physical actions. That is, perceptual cues might serve to recall motor-memory traces previously associated with a natural multisensory environment that cannot be retrieved from actual gestural knowledge. We know that effective approaches in rehabilitation are often intensive and repetitive, and therefore multisensory stimulation may facilitate the maintenance of attention and motivation in people undergoing therapy.

Studies in patients with brain damage demonstrate that both visual transitive and intransitive actions (Pazzaglia et al., 2008b), as well as hand and mouth action-related sounds, can be impaired (Pazzaglia et al., 2008a) if intentionally executed (Pazzaglia, 2013; Pazzaglia and Galli, 2014). One approach that has proven more powerful than vision alone in producing stabilized movements is using combined motor and auditory stimuli to encourage regularity of motor coordination in patients' groups (Semjen and Ivry, 2001; Thaut et al., 2002). Additionally, in the olfactory domain, individuals with autism in the presence of a facilitating olfactory cue are able to successfully initiate imitation behavior (Parma et al., 2014). Interestingly, the mere perception of breast odors in infants induces immediate motor

TABLE 1 | Summary of action observation treatment studies.

Patology	Number of participants		Sessions							
	Experimental group	Control group	Number	Duration (minutes)	Type of action	Control	Training	Re-test (days)	Generalization	Reference
Stroke	33	34	40	15	Upper limbs daily actions	Static images of objects	Imitation	120 – 150	+	Sale et al. (2014)
	28	0	20	40	Daily actions with objects		Imitation	60	+	Franceschini et al. (2010)
	11	10	12	30	Functional walking tasks	Landscape images	Imitation		+	Park et al. (2014a)
	15	15	20	40	Treadmill walking actions	Nature video	Physical + Imitation			Bang et al. (2013)
	9	9 + 9	20	30	Dynamic balance + Gait abilities	Motor imagery + Physical training	Physical + Imitation			Kim and Lee (2013)
	8	8	18	90	Daily life hand and arm actions	Geometric symbols and letters	Imitation	56	+	Ertelt et al. (2007)—fMRI
Parkinson's disease	8	8	18	40	Wii Fit game avatar actions	Rest + Motor imagery + Imitation			+	Esculier et al. (2014)—TMS
	7	8	NA	NA	Daily actions	Video clips with no motor content	Imitation		+	Buccino et al. (2011)
	10	10	12	60	Walking actions + Gait abilities	Landscape images	Imitation	28	+	Pelosin et al. (2010)
	10 + 10	14 + 8 + 10	1	6	Repetitive finger movements	Acoustic cue + Static hand	Imitation	2		Pelosin et al. (2013)
Cerebral palsy	12	12	15	60	Upper limbs daily actions	Computer games	Imitation	7 – 56 – 168	+	Sgandurra et al. (2013)
	8	7	15		Upper limbs daily actions	Video clips with no motor content	Imitation		+	Buccino et al. (2012)
	8	8	12	30	Upper limbs daily actions	Landscape images	Physical + Imitation	14	+	Kim et al. (2014a)
Orthopedic	30	30	18	24	Whole body daily actions	Video clips with no motor content	Imitation	7 – 14 – 21	+	Bellelli et al. (2010)
	9	9	9	40	Whole body daily actions	Physical training	Imitation		+	Park et al. (2014b)

responses, such as directional crawling and sucking behavior (Varendi and Porter, 2001). Moreover, an olfactory visuomotor priming paradigm can induce facilitation effects regarding the time taken to process movement, favoring less severe bradykinesia and hand movement hypometria in patients with PD (Parma et al., 2013). Therefore, it is reasonable to think that emphasizing auditory, olfactory, and somatic perception, rather than exclusively focusing on the learning of simple visual-motor skills, may be potentially useful for relearning goal-directed actions.

A multimodal approach can even be employed in simple gestures, such as eating (or re-learning to eat) an apple, which is characterized by a variety of sensory perceptions (the color of the apple, the crunchy sound of its bite, the position of the fingers to grasp the apple, and the apple's smell and taste). In this case, the motor re-education of a crucial daily life ability can be positively influenced by boosting multiple sensory modalities.

Importantly, augmenting stimulation by the combination of different modalities (olfaction, hearing, and haptics by vibrotactile actuators) may allow patients to recover lost motor functions as quickly and as permanently as possible. Indeed, multimodal integration may augment perceptual accuracy and saliency by providing redundant cues or by sustaining the missing information in perception reconstruction (Lenggenhager et al., 2013). Therefore, augmented multimodal training can reveal benefits not only in terms of outer signals, such as perceptual motor functions, but also via other neurorehabilitation interventions on inner signals involving training of motor tasks, as documented in experimental (Tsakiris et al., 2011; Ainley et al., 2014) and clinical conditions (Villiger et al., 2013; Lucci and Pazzaglia, 2015). Unfortunately, studies on the role of additive multimodal stimulation in triggering action representations during rehabilitation are currently lacking.

Although perceptual and motor event coding is crucial for shaping and implementing motor plans, knowledge about the predicted sensory and motor effects of one's movement may provide further information that is useful for controlling and adjusting representations of an intended action.

The Effect of Anticipatory Coding on Perceptual-Motor Codes

A high level of motor performance requires good ability to predict the outcomes of a motor action, which is a function that the motor system is well designed to fulfill. Important theoretical models conceptualize that the human motor system is equipped with specific, rapid, and automatic mechanisms that are crucial to the prediction of external sensory signals (Schubotz, 2007) and forthcoming motor acts, thus functioning as an anticipatory device (Wolpert and Flanagan, 2001). Studies on perceptual-motor synchronization demonstrate that action control is not sensitive to a match between sensory input and motor output, rather, it is sensitive to synchrony between the perceived sensory and motor effects of one's action, supporting the existence of an internal system that is independent of motor implementation (Sergent et al., 1993). For example, when participants are asked to tap their finger in synchrony with a periodic sequence of tones, their performance depends entirely on perceived representation. In other words, motor events are controlled by the anticipation of their effects (Repp and Penel, 2002). Clinical evidence on the prediction notion of the motor brain comes from studies conducted on patients with brain damage that suffer from action execution disorders (Fontana et al., 2012) in which there is no Readiness-Potential (RP), an electrophysiological marker of motor preparation (Schurger et al., 2012), in the spontaneous activity of their motor system. RP seems to result from forward model predictions of the motor system that automatically precede a self-initiated movement (Kilner et al., 2004). Within this context, the lack of RP exhibited by patients indicates that the inability to predict consequences of one's own motor action is directly associated with a distorted motor implementation. Efforts have been directed at bridging the discontinuities between prediction and implementation of motor actions (Wolpert and Flanagan, 2001; Iacoboni, 2003), in order to increase the anticipation of error recognition and interaction with the external world. This account of the motor system ensures that a prediction can be generalized from actions (Kilner et al., 2004) to events (Schubotz, 2007), and might benefit from multisensory stimulation that draws on the sensorimotor system.

Indeed, anticipation is also stimulated by hearing and olfaction. Memorization of the temporal association between the perception of a sound and a movement that accompanies it is a key element of learning (Aglioti and Pazzaglia, 2011). Regarding olfaction, however, odor may force us to prepare for action, adjusting the variability that is attributable to motor implementation. Such a phenomenon is documented when we smell an odor and subsequently grasp for food (Rossi et al., 2008). These are attractive examples of multi-modal prediction facilitation; however, whether and how behavioral paradigms that have been *ad hoc* devised on the basis of predictive coding algorithms will be combined with state-of-the-art neurophysiological techniques is a topic that will need to be addressed in the future.

Neural Underpinnings of Perceived and Executed Actions

Action observation treatment was inspired by studies of macaque mirror neurons, where a particular class of multimodal cells were observed to be active during action execution and action perception (di Pellegrino et al., 1992; Keysers et al., 2003). Owing to the invasiveness of the technique used to record neuron activity *in vivo*, direct evidence of double-duty visuo-motor units in humans has only been reported in one study (Mukamel et al., 2010). Neurons that share bidirectional "seeing and doing" information are located in the medial section of the frontal lobe and in the temporal cortices (Mukamel et al., 2010). However, based on the pooled responses of very large populations of neurons, non-invasive neuroimaging and transcranial magnetic stimulation (TMS) suggest a similar system of motor simulation during action observation (Fadiga et al., 1995; Buccino et al., 2001; Aziz-Zadeh et al., 2002; Gazzola and Keysers, 2009). Neural subpopulations code either perceived or executed actions that may be linked to the striking mirror property in the premotor cortex, supplementary motor area (SMA), inferior parietal lobule, cingulate gyrus, and cerebellum (Molenberghs et al., 2012).

Different cognitive neuroscience techniques and experimental protocols in healthy subjects and patients with brain damage have provided convergent evidence for the existence of a fronto-temporal-parietal network involved in a variety of sensory signals that trigger or modulate an action (Aglioti and Pazzaglia, 2010). For example, sound-into-action translation processes have been identified in the left dorsal and premotor cortices and inferior parietal lobe (Gazzola et al., 2006). Moreover, the merging of visual and auditory information enables individuals to anticipate and optimize their perceptual and motor behavior recruiting the SMA, premotor cortex and cerebellum (Chen et al., 2008). Causative information on the auditory mapping of actions has been provided by our study on patients with apraxia, where we identified a clear association between deficits in performing hand- or mouth-related actions and the ability to recognize the associated sound in the frontal cortex and parietal lobe in the left hemisphere (Pazzaglia et al., 2008a).

Even human odors communicate dynamic information about motor states (Pazzaglia, 2015). For example, a combination of olfactory and visual inputs facilitates the selection of goal-directed movements (Castiello et al., 2006), and odorant objects (for example grasping a smelled strawberry) can potentially activate the frontoparietal brain network in response to the sight of similar actions (Tubaldi et al., 2011), thus hinting at the crossmodal nature of action simulation. This bi-directional message passing in the motor system can be seen when an individual grasps for a smelled object (Rossi et al., 2008), which clearly indicates predictive coding (Tubaldi et al., 2011).

Therefore, the perception/execution system, even when apparently driven by one modality, may be largely modulated by multimodality (Pazzaglia, 2015).

Maximizing Perceptual Motor Plasticity in Rehabilitation

Neuroplastic Brain Potentialities of Observed and Executed Actions

Action-observation training promotes neural reorganization via an adaptive plasticity, which leads to behavioral success in motor performance (Wenderoth, 2015). The cortical origin of the plastic modification induced by the matching of an observed and performed action, is well illustrated by studies on system motor experts. More specifically, these studies have demonstrated that the motor repertoire "resonates" with that of observed, ongoing movements in the frontoparietal structures (Haslinger et al., 2005; Calvo-Merino et al., 2006). Moreover, after a stroke, neural changes in the motor area that are caused by observation interventions suggest a functional reorganization comparable to those evoked in the brains of expert motors. For example, TMS studies of healthy individuals and patients with brain damage (Stefan et al., 2005; Celnik et al., 2006, 2008) have provided direct evidence of increased motor cortex and cortico-spinal excitability as a result of the enhanced synaptic efficiency that reflects long-term potentiation (Rosenkranz et al., 2007). These TMS studies indicate that action observation drives reorganization in the primary motor cortex to strengthen the motor memory of an observed action in young (Stefan et al., 2005; mean age, 34 years) and elderly (Celnik et al., 2006; mean age, 65 years) subjects, as well as in patients with chronic brain damage (Celnik et al., 2008). It has also been shown that 4 weeks of active, 18-day-cycle visual/motor training significantly enhances motor function, with a significant rise in the activity of specific motor areas that possess mirror properties in patients with stroke (Ertelt et al., 2007). Conversely, massed, high-frequency rehabilitative training (300–1000 daily repetitions) based on execution alone elicits only minimal neural reorganization (Kleim et al., 2004). Further, the action-observation of grasping movements of either the right or left hand, results in increased cortico-spinal excitability when TMS activates muscles of the unaffected hand (Ertelt et al., 2007). Lateralized M1 hyperexcitability could promote plastic changes in excitatory/inhibitory circuits through cortico-cortical connections. Indeed, although selective hemispheric improvement of healthy brains undergoing motor training coupled with action observation suggests a major role of cortical activity in the left hemisphere (Hamzei et al., 2012), action observation and execution tend to be salient in both hemispheres (Gazzola et al., 2007). It is thus not surprising that after therapy, a significant increase in activity was observed in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, SMA, and contralateral supramarginal gyrus during free object manipulation in a functional magnetic resonance imaging study in stroke patients (Ertelt et al., 2007). Even in a disrupted network, enhancement of motor activity during spontaneous gestures has been observed after therapy aimed to promote adaptive neuroplasticity to enhance motor recovery (Garrison et al., 2013). Thus, the neural structures underpinning action execution observation of both hemispheres are also expected to play a role in motor recovery. Rather than employ training of a specific action observation in favor of a nonparetic limb, clinicians may point to regions activated in response to specific action observation in favor of both paretic and nonparetic limbs (Garrison et al., 2013). This supports the idea that interconnected regions of the action network can be balanced in an inhibitory manner. It is important to note that focal brain ischemia induces profound synaptic rearrangement, even in neurons adjacent to the insulted region. When the affected hemisphere undergoes long lasting increases in excitability (Manganotti et al., 2002), it influences glutamatergic synapses leading to reorganization of the peri-infarcted area (Cárdenas-Morales et al., 2010). It is also possible that the sensorimotor cortex of the affected hemisphere, through a mechanism of locally reduced transcallosal inhibition, changes the cortico-cortical excitability of the intact contralateral sensorimotor cortex. Thus, changes in inter-regional cortical excitability of a network related to a specific training program can be balanced by long-term potentiation- and depression-like processes, as well as to inhibitory mechanisms modulated by GABAergic activity stimulating a process of homeostatic metaplasticity (Ridding and Ziemann, 2010). Moreover, short-term plastic changes induced by low frequency TMS in the motor stimulation circuit can also be useful in adults with moderate to severe traumatic brain injury (Nielson et al., 2015), and in focal hand dystonia (Kimberley et al., 2015). Therefore, combined motor perception is a powerful mechanism to generalize action recovery (see **Table 1**), even if it is not related to the observed and executed stimuli used during video-therapy (Ertelt et al., 2007).

Assuming that map plasticity and motor process are interrelated, as they appear to be, then the change in excitability could inhibit or facilitate neural mechanisms underlying action execution and open up new possibilities for complementary multisensory processing with cumulative effects (Blankenburg et al., 2008).

Neuroplastic Brain Potentialities of Multimodal Actions

A prompt comparison at the cortical level between two sensorimotor representations of a movement—that which is "perceived" and that which is "performed"– is necessary to induce major plastic changes. The functional contribution of perceptual information could be extended to other modalities depending on motor connections between sensory networks. Accordingly, although unimodal input may trigger action representation, congruent multimodal input is more appropriate to provide an enriched sensory representation, which, ultimately, enables full-blown characterization of an action simulation. Moreover, different inputs could converge at the synaptic level of up-stream motor areas. For example, the pooled response of very large populations of visuo-audio-motor neurons may result in a super-additive effect; that is, stronger than the sum of the unimodal effect (Keysers et al., 2003; Kaplan and Iacoboni, 2007). In addition, the multimodal response on pooled responses of visuo-olfacto-motor populations of neurons induces further increase in activity of the simulation map.

We also suggest that the functional gain derived from multimodal integration may have origins not only in the cortex, but also induces parallel changes in spinal excitability. For example, both visual and tactile data (e.g., peripheral nerve input) lead to an increase in M1 excitability, thus inducing plasticity and encouraging the use of multimodal stimulation in clinical settings (Bisio et al., 2014). Indeed, it has been shown that 14 min of median nerve stimulation during an observed congruent movement significantly increases corticomotor excitability in the motor cortex and reduces GABAergic inhibition (Rosenkranz and Rothwell, 2003). Such changes, suggest that the re-afferent somatosensory feedback of the median nerve could generate super-additive and cumulative effects. Similarly, a clear increase in corticospinal motor facilitation during the observation of the grasping of unseen but smelt objects (Rossi et al., 2008) or during passive listening to sounds associated with bimanual actions (Aziz-Zadeh et al., 2004), has also been observed. However, neither peripheral nerve stimulation or action observation alone could induce a comparable effect. Thus, combining the re-afferent visual and somatosensory feedback of an action leads to an increase in the synaptic efficiency evoked by action execution in motor areas.

Concluding Remarks

While research on the relationship between observed and executed actions in the context of stroke treatment and rehabilitation has a short history, it has already provided new insights into the complexity of the underlying neural mechanisms of visual-motor training. The observation of actions through a process of visual retrieval and selection results in the encoding of a representation of the most probable action, providing a powerful tool for overcoming intentional motor-gestural difficulties. Moreover, tailored interventions based on an individual's ability to acquire new (or relearn old) motor-memory traces through multimodal and predictive models may be the most promising approach for the development of treatments for goal-directed action disorders.

It is clear that progress in this area, which has both theoretical and practical implications for the care of patients, requires functional and anatomical information to guide the application of rehabilitation procedures. The importance of the interplay of multiple factors, such as lesion size, lesion location, and elapsed time after stroke onset should be taken into account. It is also likely that in cases different from stroke, such as PD, cerebral palsy, and hemiparesis, these factors interact with many more unidentified elements such as age at diagnosis, disease subtype, cognitive status, and baseline motor functions. Thus, targeting rehabilitation approaches on the basis of specific brain structures that mediate the effects of latent plasticity of complex interacting networks to facilitate recovery of function is an important challenge in this growing clinical field.

Funding

MP received research support from "Sapienza" University of Rome, Grant FARI, 2011 – prot. C26I12TE94.

References

Aglioti, S. M., and Pazzaglia, M. (2010). Representing actions through their sound. *Exp. Brain Res.* 206, 141–151. doi: 10.1007/s00221-010-2344-x

Aglioti, S. M., and Pazzaglia, M. (2011). Sounds and scents in (social) action. *Trends Cogn. Sci.* 15, 47–55. doi: 10.1016/j.tics.2010.12.003

Ainley, V., Brass, M., and Tsakiris, M. (2014). Heartfelt imitation: high interoceptive awareness is linked to greater automatic imitation. *Neuropsychologia* 60, 21–28. doi: 10.1016/j.neuropsychologia.2014.05.010

Aziz-Zadeh, L., Iacoboni, M., Zaidel, E., Wilson, S., and Mazziotta, J. (2004). Left hemisphere motor facilitation in response to manual action sounds. *Eur. J. Neurosci.* 19, 2609–2612. doi: 10.1111/j.0953-816x.2004.03348.x

Aziz-Zadeh, L., Maeda, F., Zaidel, E., Mazziotta, J., and Iacoboni, M. (2002). Lateralization in motor facilitation during action observation: a TMS study. *Exp. Brain Res.* 144, 127–131. doi: 10.1007/s00221-002-1037-5

Badets, A., Blandin, Y., and Shea, C. H. (2006a). Intention in motor learning through observation. *Q. J. Exp. Psychol. (Hove)* 59, 377–386. doi: 10.1080/02724980443000773

Badets, A., Blandin, Y., Wright, D. L., and Shea, C. H. (2006b). Error detection processes during observational learning. *Res. Q. Exerc. Sport* 77, 177–184. doi: 10.5641/027013606x13080769704406

Bang, D. H., Shin, W. S., Kim, S. Y., and Choi, J. D. (2013). The effects of action observational training on walking ability in chronic stroke patients: a double-blind randomized controlled trial. *Clin. Rehabil.* 27, 1118–1125. doi: 10.1177/0269215513501528

Bassolino, M., Campanella, M., Bove, M., Pozzo, T., and Fadiga, L. (2014). Training the motor cortex by observing the actions of others during immobilization. *Cereb. Cortex* 24, 3268–3276. doi: 10.1093/cercor/bht190

Bellelli, G., Buccino, G., Bernardini, B., Padovani, A., and Trabucchi, M. (2010). Action observation treatment improves recovery of postsurgical orthopedic patients: evidence for a top-down effect? *Arch. Phys. Med. Rehabil.* 91, 1489–1494. doi: 10.1016/j.apmr.2010.07.013

Bisio, A., Avanzino, L., Gueugneau, N., Pozzo, T., Ruggeri, P., and Bove, M. (2014). Observing and perceiving: A combined approach to induce plasticity in human motor cortex. *Clin. Neurophysiol.* 126, 1212–1220. doi: 10.1016/j.clinph.2014.08.02

Blankenburg, F., Ruff, C. C., Bestmann, S., Bjoertomt, O., Eshel, N., Josephs, O., et al. (2008). Interhemispheric effect of parietal TMS on somatosensory response confirmed directly with concurrent TMS-fMRI. *J. Neurosci.* 28, 13202–13208. doi: 10.1523/JNEUROSCI.3043-08.2008

Bonifazi, S., Tomaiuolo, F., Altoè, G., Ceravolo, M. G., Provinciali, L., and Marangolo, P. (2013). Action observation as a useful approach for enhancing recovery of verb production: new evidence from aphasia. *Eur. J. Phys. Rehabil. Med.* 49, 473–481.

Brunner, I. C., Skouen, J. S., Ersland, L., and Grüner, R. (2014). Plasticity and response to action observation: a longitudinal FMRI study of potential mirror neurons in patients with subacute stroke. *Neurorehabil. Neural Repair* 28, 874–884. doi: 10.1177/1545968314527350

Buccino, G. (2014). Action observation treatment: a novel tool in neurorehabilitation. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20130185. doi: 10.1098/rstb.2013.0185

Buccino, G., Arisi, D., Gough, P., Aprile, D., Ferri, C., Serotti, L., et al. (2012). Improving upper limb motor functions through action observation treatment: a pilot study in children with cerebral palsy. *Dev. Med. Child Neurol.* 54, 822–828. doi: 10.1111/j.1469-8749.2012.04334.x

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., Gallese, V., et al. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur. J. Neurosci.* 13, 400–404. doi: 10.1111/j.1460-9568.2001.01385.x

Buccino, G., Gatti, R., Giusti, M. C., Negrotti, A., Rossi, A., Calzetti, S., et al. (2011). Action observation treatment improves autonomy in daily activities in parkinson's disease patients: results from a pilot study. *Mov. Disord.* 26, 1963–1964. doi: 10.1002/mds.23745

Buchanan, J. J., and Dean, N. J. (2010). Specificity in practice benefits learning in novice models and variability in demonstration benefits observational practice. *Psychol. Res.* 74, 313–326. doi: 10.1007/s00426-009-0254-y

Calvo-Merino, B., Grèzes, J., Glaser, D. E., Passingham, R. E., and Haggard, P. (2006). Seeing or doing? influence of visual and motor familiarity in action observation. *Curr. Biol.* 16, 1905–1910. doi: 10.1016/j.cub.2006.07.065

Cárdenas-Morales, L., Nowak, D. A., Kammer, T., Wolf, R. C., and Schönfeldt-Lecuona, C. (2010). Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr.* 22, 294–306. doi: 10.1007/s10548-009-0084-7

Casile, A., and Giese, M. A. (2006). Nonvisual motor training influences biological motion perception. *Curr. Biol.* 16, 69–74. doi: 10.1016/j.cub.2005.10.071

Castiello, U., Zucco, G. M., Parma, V., Ansuini, C., and Tirindelli, R. (2006). Cross-modal interactions between olfaction and vision when grasping. *Chem. Senses* 31, 665–671. doi: 10.1093/chemse/bjl007

Celnik, P., Stefan, K., Hummel, F., Duque, J., Classen, J., and Cohen, L. G. (2006). Encoding a motor memory in the older adult by action observation. *Neuroimage* 29, 677–684. doi: 10.1016/j.neuroimage.2005.07.039

Celnik, P., Webster, B., Glasser, D. M., and Cohen, L. G. (2008). Effects of action observation on physical training after stroke. *Stroke* 39, 1814–1820. doi: 10.1161/STROKEAHA.107.508184

Chen, J. L., Penhune, V. B., and Zatorre, R. J. (2008). Moving on time: brain network for auditory-motor synchronization is modulated by rhythm complexity and musical training. *J. Cogn. Neurosci.* 20, 226–239. doi: 10.1162/jocn.2008.20018

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., and Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp. Brain Res.* 91, 176–180. doi: 10.1007/bf00230027

Dunsky, A., Dickstein, R., Marcovitz, E., Levy, S., and Deutsch, J. E. (2008). Home-based motor imagery training for gait rehabilitation of people with chronic poststroke hemiparesis. *Arch. Phys. Med. Rehabil.* 89, 1580–1588. doi: 10.1016/j.apmr.2007.12.039

Ertelt, D., and Binkofski, F. (2012). Action observation as a tool for neurorehabilitation to moderate motor deficits and aphasia following stroke. *Neural Regen. Res.* 7, 2063–2074. doi: 10.3969/j.issn.1673-5374.2012.26.008

Ertelt, D., Hemmelmann, C., Dettmers, C., Ziegler, A., and Binkofski, F. (2012). Observation and execution of upper-limb movements as a tool for rehabilitation of motor deficits in paretic stroke patients: protocol of a randomized clinical trial. *BMC Neurol.* 12:42. doi: 10.1186/1471-2377-12-42

Ertelt, D., Small, S., Solodkin, A., Dettmers, C., McNamara, A., Binkofski, F., et al. (2007). Action observation has a positive impact on rehabilitation of motor deficits after stroke. *Neuroimage* 36(Suppl. 2), T164–T173. doi: 10.1016/j.neuroimage.2007.03.043

Esculier, J. F., Vaudrin, J., and Tremblay, L. E. (2014). Corticomotor excitability in parkinson's disease during observation, imagery and imitation of action: effects of rehabilitation using wii fit and comparison to healthy controls. *J. Parkinsons. Dis.* 4, 67–75. doi: 10.3233/JPD-130212

Fadiga, L., Fogassi, L., Pavesi, G., and Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *J. Neurophysiol.* 73, 2608–2611.

Fontana, A. P., Kilner, J. M., Rodrigues, E. C., Joffily, M., Nighoghossian, N., Vargas, C. D., et al. (2012). Role of the parietal cortex in predicting incoming actions. *Neuroimage* 59, 556–564. doi: 10.1016/j.neuroimage.2011.07.046

Franceschini, M., Agosti, M., Cantagallo, A., Sale, P., Mancuso, M., and Buccino, G. (2010). Mirror neurons: action observation treatment as a tool in stroke rehabilitation. *Eur. J. Phys. Rehabil. Med.* 46, 517–523.

Franceschini, M., Ceravolo, M. G., Agosti, M., Cavallini, P., Bonassi, S., Dall'Armi, V., et al. (2012). Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial. *Neurorehabil. Neural Repair* 26, 456–462. doi: 10.1177/1545968311427406

Garrison, K. A., Aziz-Zadeh, L., Wong, S. W., Liew, S. L., and Winstein, C. J. (2013). Modulating the motor system by action observation after stroke. *Stroke* 44, 2247–2253. doi: 10.1161/STROKEAHA.113.001105

Garrison, K. A., Winstein, C. J., and Aziz-Zadeh, L. (2010). The mirror neuron system: a neural substrate for methods in stroke rehabilitation. *Neurorehabil. Neural Repair* 24, 404–412. doi: 10.1177/1545968309354536

Gatti, R., Tettamanti, A., Gough, P. M., Riboldi, E., Marinoni, L., and Buccino, G. (2013). Action observation versus motor imagery in learning a complex motor task: a short review of literature and a kinematics study. *Neurosci. Lett.* 540, 37–42. doi: 10.1016/j.neulet.2012.11.039

Gazzola, V., Aziz-Zadeh, L., and Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. *Curr. Biol.* 16, 1824–1829. doi: 10.1016/j.cub.2006.07.072

Gazzola, V., and Keysers, C. (2009). The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. *Cereb. Cortex* 19, 1239–1255. doi: 10.1093/cercor/bhn181

Gazzola, V., van der Worp, H., Mulder, T., Wicker, B., Rizzolatti, G., and Keysers, C. (2007). Aplasics born without hands mirror the goal of hand actions with their feet. *Curr. Biol.* 17, 1235–1240. doi: 10.1016/j.cub.2007.06.045

Hamzei, F., Läppchen, C. H., Glauche, V., Mader, I., Rijntjes, M., and Weiller, C. (2012). Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere. *Neurorehabil. Neural Repair* 26, 484–496. doi: 10.1177/1545968311427917

Haslinger, B., Erhard, P., Altenmüller, E., Schroeder, U., Boecker, H., and Ceballos-Baumann, A. O. (2005). Transmodal sensorimotor networks during action observation in professional pianists. *J. Cogn. Neurosci.* 17, 282–293. doi: 10.1162/0898929053124893

Hecht, H., Vogt, S., and Prinz, W. (2001). Motor learning enhances perceptual judgment: a case for action-perception transfer. *Psychol. Res.* 65, 3–14. doi: 10.1007/s004260000043

Heyes, C. M., and Foster, C. L. (2002). Motor learning by observation: evidence from a serial reaction time task. *Q. J. Exp. Psychol. A* 55, 593–607. doi: 10.1080/02724980143000389

Hommel, B. (1996). The cognitive representation of action: automatic integration of perceived action effects. *Psychol. Res.* 59, 176–186. doi: 10.1007/bf00425832

Hotz-Boendermaker, S., Hepp-Reymond, M. C., Curt, A., and Kollias, S. S. (2011). Movement observation activates lower limb motor networks in chronic complete paraplegia. *Neurorehabil. Neural Repair* 25, 469–476. doi: 10.1177/1545968310389184

Iacoboni, M. (2003). "Understanding others: imitation, language, empathy," in *Perspectives on Imitation: From Cognitive Neuroscience to Social Science, Volume 1: Mechanisms of Imitation and Imitation in Animals*, 1st Edn, eds S. Hurley and N. Chater (Cambridge, MA: MIT Press), 77–100.

Ietswaart, M., Johnston, M., Dijkerman, H. C., Joice, S., Scott, C. L., MacWalter, R. S., et al. (2011). Mental practice with motor imagery in stroke recovery: randomized controlled trial of efficacy. *Brain* 134, 1373–1386. doi: 10.1093/brain/awr077

Kantak, S. S., and Winstein, C. J. (2012). Learning-performance distinction and memory processes for motor skills: a focused review and perspective. *Behav. Brain Res.* 228, 219–231. doi: 10.1016/j.bbr.2011.11.028

Kaplan, J. T., and Iacoboni, M. (2007). Multimodal action representation in human left ventral premotor cortex. *Cogn. Process.* 8, 103–113. doi: 10.1007/s10339-007-0165-z

Keysers, C., Kohler, E., Umiltà, M. A., Nanetti, L., Fogassi, L., and Gallese, V. (2003). Audiovisual mirror neurons and action recognition. *Exp. Brain Res.* 153, 628–636. doi: 10.1007/s00221-003-1603-5

Kilner, J. M., Vargas, C., Duval, S., Blakemore, S. J., and Sirigu, A. (2004). Motor activation prior to observation of a predicted movement. *Nat. Neurosci.* 7, 1299–1301. doi: 10.1038/nn1355

Kim, J. Y., Kim, J. M., and Ko, E. Y. (2014a). The effect of the action observation physical training on the upper extremity function in children with cerebral palsy. *J. Exerc. Rehabil.* 10, 176–183. doi: 10.12965/jer.140114

Kim, S. S., Kim, T. H., and Lee, B. H. (2014b). Effects of Action Observational Training on Cerebral Hemodynamic Changes of Stroke Survivors: A fTCD Study. *J. Phys. Ther. Sci.* 26, 331–334. doi: 10.1589/jpts.26.331

Kim, J. H., and Lee, B. H. (2013). Action observation training for functional activities after stroke: a pilot randomized controlled trial. *Neurorehabilitation* 33, 565–574. doi: 10.3233/NRE-130991

Kimberley, T. J., Borich, M. R., Schmidt, R. L., Carey, J. R., and Gillick, B. (2015). Focal hand dystonia: individualized intervention with repeated application of repetitive transcranial magnetic stimulation. *Arch. Phys. Med. Rehabil.* 96, S122–S128. doi: 10.1016/j.apmr.2014.07.426

Kleim, J. A., Hogg, T. M., Vandenberg, P. M., Cooper, N. R., Bruneau, R., and Remple, M. (2004). Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *J. Neurosci.* 24, 628–633. doi: 10.1523/jneurosci.3440-03.2004

Lenggenhager, B., Scivoletto, G., Molinari, M., and Pazzaglia, M. (2013). Restoring tactile awareness through the rubber hand illusion in cervical spinal cord injury. *Neurorehabil. Neural Repair* 27, 704–708. doi: 10.1177/1545968313491009

Lucci, G., and Pazzaglia, M. (2015). Towards multiple interactions of inner and outer sensations in corporeal awareness. *Front. Hum. Neurosci.* 9:163. doi: 10.3389/fnhum.2015.00163

Manganotti, P., Patuzzo, S., Cortese, F., Palermo, A., Smania, N., and Fiaschi, A. (2002). Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. *Clin. Neurophysiol.* 113, 936–943. doi: 10.1016/s1388-2457(02)00062-7

Mann, D. L., Abernethy, B., and Farrow, D. (2010). Visual information underpinning skilled anticipation: the effect of blur on a coupled and uncoupled in situ anticipatory response. *Atten. Percept. Psychophys.* 72, 1317–1326. doi: 10.3758/APP.72.5.1317

Marangon, M., Priftis, K., Fedeli, M., Masiero, S., Tonin, P., and Piccione, F. (2014). Lateralization of motor cortex excitability in stroke patients during action observation: a TMS study. *Biomed Res. Int.* 2014:251041. doi: 10.1155/2014/251041

Molenberghs, P., Cunnington, R., and Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci. Biobehav. Rev.* 36, 341–349. doi: 10.1016/j.neubiorev.2011.07.004

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., and Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. *Curr. Biol.* 20, 750–756. doi: 10.1016/j.cub.2010.02.045

Nielson, D. M., McKnight, C. A., Patel, R. N., Kalnin, A. J., and Mysiw, W. J. (2015). Preliminary guidelines for safe and effective use of repetitive transcranial magnetic stimulation in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 96, S138–S144. doi: 10.1016/j.apmr.2014.09.010

Page, S. J., Levine, P., Sisto, S., and Johnston, M. V. (2001). A randomized efficacy and feasibility study of imagery in acute stroke. *Clin. Rehabil.* 15, 233–240. doi: 10.1191/026921501672063235

Park, H. R., Kim, J. M., Lee, M. K., and Oh, D. W. (2014a). Clinical feasibility of action observation training for walking function of patients with post-stroke hemiparesis: a randomized controlled trial. *Clin. Rehabil.* 28, 794–803. doi: 10.1177/0269215514523145

Park, S. D., Song, H. S., and Kim, J. Y. (2014b). The effect of action observation training on knee joint function and gait ability in total knee replacement patients. *J. Exerc. Rehabil.* 10, 168–171. doi: 10.12965/jer.140112

Parma, V., Bulgheroni, M., Scaravilli, T., Tirindelli, R., and Castiello, U. (2013). Implicit olfactory processing attenuates motor disturbances in idiopathic parkinson's disease. *Cortex* 49, 1241–1251. doi: 10.1016/j.cortex.2012.05.017

Parma, V., Bulgheroni, M., Tirindelli, R., and Castiello, U. (2014). Facilitation of action planning in children with autism: the contribution of the maternal body odor. *Brain Cogn.* 88, 73–82. doi: 10.1016/j.bandc.2014.05.002

Pazzaglia, M. (2013). Does what you hear predict what you will do and say? *Behav. Brain Sci.* 36, 370–371. doi: 10.1017/S0140525X12002804

Pazzaglia, M. (2015). Body and odors: non just molecules, after all. *Curr. Dir. Psychol. Sci.* 24, 329–333. doi: 10.1177/0963721415575329

Pazzaglia, M., and Galli, G. (2014). Loss of agency in apraxia. *Front. Hum. Neurosci.* 8:751. doi: 10.3389/fnhum.2014.00751

Pazzaglia, M., Pizzamiglio, L., Pes, E., and Aglioti, S. M. (2008a). The sound of actions in apraxia. *Curr. Biol.* 18, 1766–1772. doi: 10.1016/j.cub.2008.09.061

Pazzaglia, M., Smania, N., Corato, E., and Aglioti, S. M. (2008b). Neural underpinnings of gesture discrimination in patients with limb apraxia. *J. Neurosci.* 28, 3030–3041. doi: 10.1523/JNEUROSCI.5748-07.2008

Pelosin, E., Avanzino, L., Bove, M., Stramesi, P., Nieuwboer, A., and Abbruzzese, G. (2010). Action observation improves freezing of gait in patients with parkinson's disease. *Neurorehabil. Neural Repair* 24, 746–752. doi: 10.1177/1545968310368685

Pelosin, E., Bove, M., Ruggeri, P., Avanzino, L., and Abbruzzese, G. (2013). Reduction of bradykinesia of finger movements by a single session of action observation in parkinson disease. *Neurorehabil. Neural Repair* 27, 552–560. doi: 10.1177/1545968312471905

Pomeroy, V. M., Clark, C. A., Miller, J. S., Baron, J. C., Markus, H. S., and Tallis, R. C. (2005). The potential for utilizing the "mirror neurone system" to enhance recovery of the severely affected upper limb early after stroke: a review and hypothesis. *Neurorehabil. Neural Repair* 19, 4–13. doi: 10.1177/1545968304274351

Prinz, W. (1990). "A common coding approach to perception and action," in *Relationships Between Perception and Action*, eds O. Neumann and W. Prinz (New York, NY: Springer), 167–201.

Repp, B. H., and Penel, A. (2002). Auditory dominance in temporal processing: new evidence from synchronization with simultaneous visual and auditory sequences. *J. Exp. Psychol. Hum. Percept. Perform.* 28, 1085–1099. doi: 10.1037/0096-1523.28.5.1085

Ridding, M. C., and Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *J. Physiol.* 588, 2291–2304. doi: 10.1113/jphysiol.2010.190314

Rosenkranz, K., and Rothwell, J. C. (2003). Differential effect of muscle vibration on intracortical inhibitory circuits in humans. *J. Physiol.* 551, 649–660. doi: 10.1113/jphysiol.2003.043752

Rosenkranz, K., Williamon, A., and Rothwell, J. C. (2007). Motorcortical excitability and synaptic plasticity is enhanced in professional musicians. *J. Neurosci.* 27, 5200–5206. doi: 10.1523/jneurosci.0836-07.2007

Rossi, S., De Capua, A., Pasqualetti, P., Ulivelli, M., Fadiga, L., Falzarano, V., et al. (2008). Distinct olfactory cross-modal effects on the human motor system. *PLoS One* 3:e1702. doi: 10.1371/journal.pone.0001702

Sale, P., Ceravolo, M. G., and Franceschini, M. (2014). Action observation therapy in the subacute phase promotes dexterity recovery in right-hemisphere stroke patients. *Biomed Res. Int.* 2014:457538. doi: 10.1155/2014/457538

Sale, P., and Franceschini, M. (2012). Action observation and mirror neuron network: a tool for motor stroke rehabilitation. *Eur. J. Phys. Rehabil. Med.* 48, 313–318.

Schubotz, R. I. (2007). Prediction of external events with our motor system: towards a new framework. *Trends Cogn. Sci.* 11, 211–218. doi: 10.1016/j.tics.2007.02.006

Schurger, A., Sitt, J. D., and Dehaene, S. (2012). An accumulator model for spontaneous neural activity prior to self-initiated movement. *Proc. Natl. Acad. Sci. U S A* 109, E2904–E2913. doi: 10.1073/pnas.1210467109

Semjen, A., and Ivry, R. B. (2001). The coupled oscillator model of between-hand coordination in alternate-hand tapping: a reappraisal. *J. Exp. Psychol. Hum. Percept. Perform.* 27, 251–265. doi: 10.1037/0096-1523.27.2.251

Sergent, V., Hellige, J. B., and Cherry, B. (1993). Effects of responding hand concurrent verbal processing on time-keeping and motor-implementation processes. *Brain Cogn.* 23, 243–262. doi: 10.1006/brcg.1993.1058

Sgandurra, G., Ferrari, A., Cossu, G., Guzzetta, A., Biagi, L., Tosetti, M., et al. (2011). Upper limb children action-observation training (UP-CAT): a randomised controlled trial in hemiplegic cerebral palsy. *BMC Neurol.* 11:80. doi: 10.1186/1471-2377-11-80

Sgandurra, G., Ferrari, A., Cossu, G., Guzzetta, A., Fogassi, L., and Cioni, G. (2013). Randomized trial of observation and execution of upper extremity actions versus action alone in children with unilateral cerebral palsy. *Neurorehabil. Neural Repair* 27, 808–815. doi: 10.1177/1545968313497101

Small, S. L., Buccino, G., and Solodkin, A. (2012). The mirror neuron system and treatment of stroke. *Dev. Psychobiol.* 54, 293–310. doi: 10.1002/dev.20504

Small, S. L., Buccino, G., and Solodkin, A. (2013). Brain repair after stroke—a novel neurological model. *Nat. Rev. Neurol.* 9, 698–707. doi: 10.1038/nrneurol.2013.222

Stefan, K., Cohen, L. G., Duque, J., Mazzocchio, R., Celnik, P., Sawaki, L., et al. (2005). Formation of a motor memory by action observation. *J. Neurosci.* 25, 9339–9346. doi: 10.1523/jneurosci.2282-05.2005

Thaut, M. H., Kenyon, G. P., Hurt, C. P., McIntosh, G. C., and Hoemberg, V. (2002). Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. *Neuropsychologia* 40, 1073–1081. doi: 10.1016/s0028-3932(01)00141-5

Tsakiris, M., Tajadura-Jiménez, A., and Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proc. Biol. Sci.* 278, 2470–2476. doi: 10.1098/rspb.2010.2547

Tubaldi, F., Turella, L., Pierno, A. C., Grodd, W., Tirindelli, R., and Castiello, U. (2011). Smelling odors, understanding actions. *Soc. Neurosci.* 6, 31–47. doi: 10.1080/17470911003691089

Varendi, H., and Porter, R. H. (2001). Breast odour as the only maternal stimulus elicits crawling towards the odour source. *Acta Paediatr.* 90, 372–375. doi: 10.1111/j.1651-2227.2001.tb00434.x

Villiger, M., Bohli, D., Kiper, D., Pyk, P., Spillmann, J., Meilick, B., et al. (2013). Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. *Neurorehabil. Neural Repair* 27, 675–683. doi: 10.1177/1545968313490999

Wenderoth, M. (2015). Changing the brain with multimodal mirrors: combining visual and somatosensory stimulation to enhance motor plasticity. *Clin. Neurophysiol.* 126, 1065–1066. doi: 10.1016/j.clinph.2014.09.024

Wolpert, D. M., and Flanagan, J. R. (2001). Motor prediction. *Curr. Biol.* 11, R729–R732. doi: 10.1016/S0960-9822(01)00432-8

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 02 June 2015
doi: 10.3389/fnbeh.2015.00147

Neuroplastic effects of transcranial near-infrared stimulation (tNIRS) on the motor cortex

Leila Chaieb [1,2†], Andrea Antal [1†], Florentin Masurat [1] and Walter Paulus [1]*

[1] Department of Clinical Neurophysiology, Georg-August University, Göttingen, Germany, [2] Department of Epileptology, University of Bonn, Bonn, Germany

Near-infrared light stimulation of the brain has been claimed to improve deficits caused by traumatic brain injury and stroke. Here, we exploit the effect of transcranial near-infrared stimulation (tNIRS) as a tool to modulate cortical excitability in the healthy human brain. tNIRS was applied at a wavelength of 810 nm for 10 min over the hand area of the primary motor cortex (M1). Both single-pulse and paired-pulse measures of transcranial magnetic stimulation (TMS) were used to assess levels of cortical excitability in the corticospinal pathway and intracortical circuits. The serial reaction time task (SRTT) was used to investigate the possible effect of tNIRS on implicit learning. By evaluating the mean amplitude of single-pulse TMS elicited motor-evoked-potentials (MEPs) a significant decrease of the amplitude was observed up to 30 min post-stimulation, compared to baseline. Furthermore, the short interval cortical inhibition (SICI) was increased and facilitation (ICF) decreased significantly after tNIRS. The results from the SRTT experiment show that there was no net effect of stimulation on the performance of the participants. Results of a study questionnaire demonstrated that tNIRS did not induce serious side effects apart from light headache and fatigue. Nevertheless, 66% were able to detect the difference between active and sham stimulation conditions. In this study we provide further evidence that tNIRS is suitable as a tool for influencing cortical excitability and activity in the healthy human brain.

Keywords: neuroplasticity, transcranial near-infrared laser light stimulation, brain, learning, human

OPEN ACCESS

Edited by:
Benedetto Sacchetti,
University of Turin, Italy

Reviewed by:
Marco Cambiaghi,
University of Turin, Italy
Thomas Zandonai,
University of Verona, Italy

Correspondence:
Andrea Antal,
Department of Clinical Neurophysiology, Georg-August University, Robert-Koch-Street 40, 37075 Göttingen, Germany
aantal@gwdg.de

† These authors have contributed equally to this work.

Received: *11 March 2015*
Accepted: *18 May 2015*
Published: *02 June 2015*

Citation:
Chaieb L, Antal A, Masurat F and Paulus W (2015) Neuroplastic effects of transcranial near-infrared stimulation (tNIRS) on the motor cortex. Front. Behav. Neurosci. 9:147. doi: 10.3389/fnbeh.2015.00147

Introduction

The transcranial application of near infrared light (tNIRS) to tissues in both the peripheral and the central nervous system (CNS) has been performed for at least a decade and stimulation parameters like wavelength, fluence, irradiance, treatment duration and timing, continuous or pulsed stream of laser light have been investigated, mainly in animal models (Bjordal et al., 2003; Ilic et al., 2006; Huang et al., 2009). A U-shaped response curve characterizes the optimum dosage of laser light promoting wound healing and regeneration of tissue, while a higher dosage has a detrimental effect due to heating of the tissue (Huang et al., 2009; Hashmi et al., 2010a,b; Chung et al., 2012).

Abbreviations: AMT, active motor thresholds; CCO, cytochrome C oxidase; EMG, electromyogram; FDI, first dorsal interosseous muscle; ICF, intracortical facilitation; ISI, interstimulus intervals; M1, primary motor cortex; MEP, motor evoked potential; RMT, resting motor threshold; SICI, short intracortical inhibition; SRTT, serial reaction time task; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tNIRS, transcranial near-infrared stimulation; TMS, transcranial magnetic stimulation; tRNS, transcranial random noise stimulation.

The primary target of applying infrared light as a therapeutic tool is for wound healing, inflammation and chronic pain relief. Applications have been widened to include the potential of rehabilitative treatment for neurological disorders, which has been extensively investigated using animal models (Detaboada et al., 2006; Oron et al., 2006, 2012), in clinical trials of patients with stroke and traumatic brain injury (Lampl et al., 2007; Hashmi et al., 2010a; Stemer et al., 2010; Naeser et al., 2011; Zivin et al., 2014), as well as showing promise as a potential treatment for Alzheimer's disease (Sommer et al., 2012). tNIRS therapies, applied in optimized dosages have been claimed to produce remarkable and reproducible effects both in the brain and peripheral tissues after traumatic insult in both animal models of disease and in humans (Gigo-Benato et al., 2005; Ilic et al., 2006; Naeser et al., 2011). The outcomes of these studies have led to the establishment of a multinational stroke trial (NCT01120301) to investigate the application of tNIRS in stroke rehabilitation and its ability to limit cognitive deficits post stroke onset (Lampl et al., 2007; Stemer et al., 2010; Zivin et al., 2014).

The putative mechanism of action of infrared light is believed potentiate the cytochrome C oxidase (CCO or complex IV) complex in the mitochondria, a component of the electron transport chain and key complex in ATP production. The action spectrum of CCO is in the near-infrared range. As tNIRS is applied at a wavelength of 810 nm, this suggests that CCO might play a key role in the cellular response of the stimulation (Karu, 1987). *In vitro* experiments have shown that laser irradiation modulates mitochondrial respiration levels, and is increased following irradiation of cellular tissues, causing an amplification of mitochondrial products, such as ATP, nicotinamide adenine dinucleotide (NADH), protein and ribonucleic acid (RNA) (Karu, 1999). tNIRS could increase the process of cellular respiration in neurons by increasing energy and cyclic adenosine monophosphate (cAMP) levels and indirectly, modulate the activity of neurons. Konstantinovic et al. (2013) in a previous study extended this view by highlighting the role of changing intracellular calcium concentration due to cortical trauma, and the modulation of $Na^{+}K^{+}$—ATPase activity associated with neurological pathologies, like stroke and traumatic brain injury. They hypothesized that application of tNIRS has a membrane stabilizing effect and (the increased activity of the Na^{+} pumps due to laser light irradiation underlies these stabilization effects) that may be an important contributing factor behind the positive clinical effects reported in earlier acute stroke studies. Next to the potential role of CCO in the effect of tNIRS a second putative mechanism of how near-infrared light can affect neurons is through the dissociation of nitric oxide (NO) and oxygen (Hashmi et al., 2010a). NO is an important cellular signaling molecule, and is also a potent neurotransmitter in the CNS, which is capable of inducing synaptic plasticity (Iino, 2006). By the action of laser induced NO dissociation from the CCO complex, the ongoing cellular respiration rate in the mitochondria can continue unhindered, even under conditions of stress (Karu, 1989).

tNIRS is technically similar to the near-infrared spectroscopy (NIRS) that is a widely applied non-invasive method for studying functional activation through monitoring changes in the hemodynamic properties of the brain, at least with regard to the wavelength of the applied light (Villringer et al., 1993). However, in the case of NIRS the power level of the stimulation is highly depends on the type of application and the number sources (up to 500 mW).

Here, we provide evidence that tNIRS is suitable as a tool for influencing cortical excitability and activity in the healthy human brain. A previous study has already reported that infrared stimulation can decrease motor cortical excitability in healthy subjects (Konstantinovic et al., 2013). In order to replicate and extend these data we have applied tNIRS over the cortical representation of the hand area of the primary motor cortex (M1) using a constellation of four laser diodes attached to percutaneous acupuncture needles. With this study we aimed to investigate whether tNIRS was (i) able to modulate patterns of cortical excitability (single-pulse measures of cortical excitability); (ii) which intracortical neural circuits were affected by this form of stimulation using paired-pulse measures; and lastly (iii) whether any change in performance on the behavioral or cognitive levels could be detected (using the SRTT). This final objective is very relevant to studies investigating the effects of near-infrared laser light stimulation on the intact and damaged cortex in patients suffering from stroke related pathologies or patients who have been treated for traumatic brain injury (Gur et al., 2007; Lampl et al., 2007; Hashmi et al., 2010a; Naeser et al., 2011).

Materials and Methods

The study was approved by the ethics committee of the University of Göttingen and conformed to the Declaration of Helsinki. All participants were informed as to all aspects of the experiments and gave written consent.

Subjects

Altogether 55 right handed volunteers in the age range of 18–35 years were recruited, passed a standard physician's examination and met further inclusion criteria: no neurological or psychiatric disorders, pacemaker, metal implants in the head region, pregnancy, drug or alcohol addiction, or participation in another study within the last 6 weeks.

Transcranial Near-infrared Laser Stimulation (tNIRS)

tNIRS was applied using a continuous wave diverging laser beam, with an increase in diameter of the beam width of 2 mm with every 1 cm increase along its path length. There are currently no protocols exist in a healthy population, in which the factors (intensity, power, duration, and fluence of the laser light etc.) of the stimulation are defined in detail. Therefore, there is no consensus as to which parameters should be selected for stimulation of the intact cortex in order for the near-infrared laser light to optimally stimulate the target cortical area. According to our laboratory measurements and data from a previous study (Litscher and Litscher, 2013), the penetration of the infrared light through the skull (6–7 mm thickness) is about 1–5%. Depending on the thickness of the skin (for which every mm half of the irradiated energy of the beam is absorbed) and cerebrospinal fluid (CSF), only a small fraction of the emitted laser light energy can reach the cortical surface. Our stimulation parameters were thus: we have used a total power of 150 mW over an area of 0.35 cm^2, which equates to a power density of 500 mW/cm^2 on the surface of the skin, resulting in less than 5 mW/cm^2 cortical fluence (∼ 1 J total energy). The temperature increase on the skin under the diodes was max 1°C. This value is lower than can be measured during the application of other NIR light-based applications, such as pulse oximetry, NIRS and diffuse optical tomography (Bozkurt and Onaral, 2004). In previous studies similar stimulation intensity values were used with an even longer stimulation duration (20 min) applying stimulation over the center of the scalp for treating burnout syndrome (Litscher et al., 2013). Other studies investigating the treatment of patients with traumatic brain injury or depression used a 500 mW total energy dose (Naeser et al., 2011; Naeser and Hamblin, 2011) or a calculated cortical power density of 9.5 mW/cm^2 (Schiffer et al., 2009). According to the later study the output of the device they used was "at least 5 times less than the PhotoThera laser device (personal communication, Luis DeTaboada, PhotoThera Inc, Carlsbad, CA) that was used without observed side-effects in stroke patients" (Lampl et al., 2007).

tNIRS was applied using four stainless steel laser acupuncture diode needles, which were sterilized after each use. The laser needles were placed in a square over the M1, at the "hotspot" predetermined by TMS (see below) and held in place with wire holders attached to a crown that wraps around the head of the participant (**Figure 1**). The diodes did not touch the skin or each other, there was 5 mm distance between the skin and between the diodes. In order to exclude the unspecific effects of the stimulation, eight subjects participated in a control condition, in which the same laser needles were placed over the Oz electrode position (see below).

The laser stimulator (WeberMedical, GmbH; Klasse 1, Type BF, Laser Class 3B, max power for infrared 100 mW/diode; with certifications for human applications, including stimulation of the scalp, in the EU and USA) was programmed to administer tNIRS for 10 min; once the preset duration has been reached, the stimulation is terminated automatically. All four needles were active during stimulation producing about 150 mW energy. In each experiment subjects had to participate in 2 experimental sessions, receiving either placebo or active stimulation in a randomized counterbalanced order. During the placebo condition the laser was switched on for a 30 s period only. A minimum of 4 days were maintained between each experimental session to avoid any carry-over effects of the stimulation.

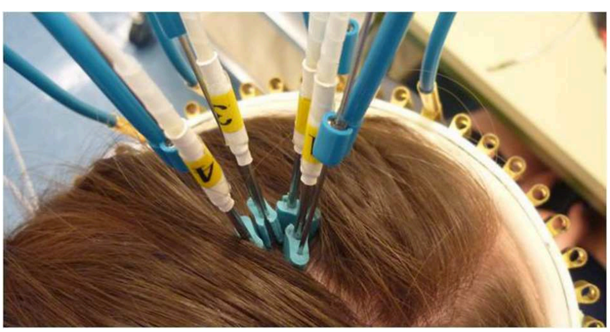


FIGURE 1 | tNIRS head montage. The laser acupuncture needles are fixed to scalp with the crown and the bendable wire holding mechanism. The waves are carried via optical fibers to the stainless steel percutaneous needles.

Measurement of Motor-cortical Excitability

To detect changes in excitability motor-evoked-potentials (MEPs) of the right first dorsal interosseous (FDI) were recorded following tNIRS of its motor-cortical representational field by single-pulse TMS. These were elicited using a Magstim 200 magnetic stimulator (Magstim, Whiteland, Dyfed, UK) and a figure-of-eight magnetic coil (diameter of one winding = 70 mm; peak magnetic field = 2.2 Tesla). The coil was held tangentially to the skull, with the handle pointing backwards and laterally at 45° from the midline. The optimal position was defined as the site where stimulation resulted consistently in the largest MEP. Surface electromyogram (EMG) was recorded from the right FDI with Ag–AgCl electrodes in a belly tendon montage. Raw signals were amplified, band-pass filtered (2 Hz–3 kHz; sampling rate 5 kHz), digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) controlled by Signal Software (Cambridge Electronic Design, version 2.13) and stored on a personal computer for offline analysis. The intensity of the stimulator output was adjusted for baseline recording so that the average stimulus led to an MEP of 1 mV in amplitude.

Resting motor threshold (RMT), active motor threshold (AMT), the intensity required to elicit an MEP of ∼1 mV peak-to-peak amplitude (SI1 mV) and a baseline of TMS-evoked MEPs at the defined SI1 mV intensity, were recorded at 0.25 Hz prior to stimulation. Stimulus intensities (in percentage of maximal stimulator output) of TMS were determined at the beginning of each experiment. RMT was defined as the minimal output of the stimulator that induced a reliable MEP (50 μV) in at least three of six consecutive trials when the FDI muscle was completely relaxed. AMT was defined as the lowest stimulus intensity at which three of six consecutive stimuli elicited reliable MEPs (200 μV) in the tonically contracting FDI muscle (Rothwell, 1999).

Experimental Procedures

We had three experimental sessions: (1) single pulse MEP measurements were introduced in order to measure corticospinal excitability (15 subjects, 7 males stimulating the M1 and 8 subjects, 3 males stimulating the visual cortex); (2) paired- pulse TMS was applied in order to measure intracortical (15 subjects, 7 males); (3) implicit motor learning task was used to test if tNIRS can modulate motor learning (32 subjects, 16 males). The experiments were conducted in a randomized, repeated measurement design, on different experimental days, separated at least with a weak pause.

Measuring Corticospinal Excitability

Before tNIRS TMS-evoked MEPs (30 stimuli) were recorded at 0.25 Hz. Baseline measurement was followed by 10 min active or sham tNIRS. After termination of tNIRS, 30 MEPs were recorded at 0 min, 5–30 min and then every 10–60 min poststimulation.

Measures of Intracortical Excitability

Short intracortical inhibition (SICI), intracortical facilitation (ICF) and long intracortical inhibition (LICI) were measured prior to active and sham stimulation sessions, immediately and 30 min poststimulation. The following protocols were used: for SICI/ICF, two magnetic stimuli were given through the same stimulating coil, and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated (Kujirai et al., 1993). To avoid any floor or ceiling effect, the intensity of the conditioning stimulus was set to 80% of AMT. The test-stimulus intensity was adjusted to SI1 mV. SICI was measured with interstimulus intervals (ISI) of 2 and 4 ms and ICF with ISIs of 7, 9, and 12 ms. At each time points the conditioning-test stimuli were recoded 20 times. The mean peak-to-peak amplitude of the conditioned MEP at each ISI was expressed as a percentage of the mean peak-to-peak size of the unconditioned test pulse.

The second protocol tested was LICI, which applies two suprathreshold stimuli with ISIs of 50, 100, 150, and 200 ms (Valls-Sole et al., 1992). The intensity of both stimuli was set to 110% of RMT. LICI was taken as the mean percentage inhibition of the conditioned test pulse MEP at ISIs of 50, 100, 150, and 200 ms. At each time points the conditioning-test stimuli were recoded 20 times.

Investigating Implicit Motor Learning Using a Serial Reaction Time Task (SRTT)

The SRTT (Nissen and Bullmer, 1987) is an established test to investigate implicit motor learning also in the context of brain stimulation (Nitsche et al., 2003) During the task the participant has to respond to a visual cue as fast and as accurately as possible with individual finger movements in response to a four dot sequence on the computer screen. Participants are unaware that the sequences follow a pseudo-repeating pattern, but their ability to implicitly "learn" the sequence is measured over the course of the task. The task is divided into 8 blocks. Blocks 1–5 and blocks 7 and 8 have the same pattern, whereas the sequence in block 6 is different to the other sequences presented in the other blocks. The calculated difference in the participants' reaction times in block 6 compared to their performance in block 7 is considered to be a measure of implicit motor-learning. Effects of transcranial stimulation using the SRTT have been shown to be a robust measure of this kind of learning and the structure of the paradigm ensures a specific sequence learning is measured and prevents an unspecific decreased reaction time purely due to increasing task routine (Pascual-Leone et al., 1994).

The subjects were seated in front of a computer screen placed at eye level and were not informed as to the aim of the SRTT. Their right fingers were placed on the computer keyboard on the designated keys for each finger. Four bars appeared on the screen: the first from the left corresponding to the right index finger, the second the middle finger, the third the ring finger and the fourth the little finger. The SRTT was performed using windows-based software using a modified standard keyboard in which only the buttons assigned for active button presses were present. For purpose of the task, this experimental setup was adequate for examining the differences in RTs of participants before and during tNIRS. Ten minutes tNIRS or sham stimulation was given during the performance of the task. In each trial, RT was measured from the appearance of the "go" signal until the first button was pushed by the subject. For each block of trials in a given experimental condition, mean RT was calculated for each subject separately.

Questionnaires

To examine safety aspects and to evaluate the blinding efficacy of tNIRS, participants were asked to fill out questionnaires examining the cutaneous effects of tNIRS in the SRTT task. Side effects like heating sensations, tingling, itching and pain, fatigue, nervousness and differences in concentration as well as any other noticeable sensations were documented. The questions concerned sensations during and after (2–6 min) the stimulation. 28 questionnaires were filled out correctly (15 active and 13 sham sessions).

Data Analyses

Single-pulse TMS

MEP amplitude means were calculated for each time point covering baseline (30 stimuli) and poststimulation time-points (30 stimuli). Baseline normalized MEPs were analyzed using repeated measurements of ANOVA (CONDITION (tNIRS vs. sham) × TIME (0, 5, 10, 15; 20, 25; 30, 40, 50, 60 min post-stimulation). Effects were considered significant if $p < 0.05$. In the case of a significant main effect or interaction, a Student's *t*-test was performed. Student's *t*-test was used to compare the MEP values between baseline and post-stimulation measurements within group. All data are given as means + SEM.

Paired-pulse TMS

For each measurement [SICI, LICI, input-output curves (I/O)], we performed separate analyses of variance (ANOVAs) for repeated measurements by using the mean values from each subject as the dependent variable. In addition to the factor CONDITION (tNIRS vs. sham), the ANOVA model included the factor "ISI" when SICI/ICF (2, 4, 7, 9, 12) or LICI (50, 100, 150, 200) were analyzed. With regard to recruitment curves the factor "intensity" (100%, 130%, and 150% of RMT) was considered. A p value of <0.05 was considered significant for all statistical analyses. In the case of a significant main effect or interaction between ISI/intensity and stimulation condition, a Student's *t*-test was performed.

SRTT Analysis

A repetitive measures ANOVA (independent variables: CONDITION and BLOCK) for reaction time (RT) and error rate (ER) was performed. As the RT difference between Block 5 and 6 is thought to represent an exclusive measure of implicit learning, Students' *t*-tests were performed to compare the respective differences between tNIRS and sham conditions. A p value of <0.05 was considered significant for all statistical analyses.

Results

All of the subjects tolerated the stimulation; none of the experimental sessions were interrupted or terminated due to side effects of the stimulation.

RMT, AMT, SICI, ICF, LICI curve baseline values were compared between tNIRS and sham conditions using Student's *t*-test. There was no significant difference in any of the measurements (all ps > 0.3).

Single-pulse MEPs

After 10 min tNIRS cortical excitability decreased by 20–30%, as revealed by single-pulse TMS. According to the *t*-test, significantly decreased MEPs were observed at the 0 and 30 min compared to the baseline ($p < 0.05$). Repeated measurements of ANOVA revealed a significant main effect of CONDITION [$F_{(1, 14)} = 10.21$, $p = 0.006$]. The main effect of TIME [$F_{(9, 126)} = 1.33$, $p = 0.23$] and the interaction between CONDITION and TIME were not significant [$F_{(9, 126)} = 0.73$, $p = 0.67$] (**Figure 2A**). Individual data can be seen on **Figures 2B,C**.

The stimulation of the visual area did not result in any MEP change, compared to the sham condition [CONDITION: $F_{(1, 7)} = 0.21$, $p = 0.66$; TIME: $F_{(9, 63)} = 0.73$, $p = 0.68$; CONDITION × TIME: $F_{(9, 63)} = 1.21$, $p = 0.3$].

Paired-pulse TMS

With regard to SICI repeated measurements of ANOVA revealed a significant effect of ISI [$F_{(4, 48)} = 63.81$, $p < 0.001$] and CONDITION [$F_{(1, 12)} = 7.99$, $p = 0.015$], which was due to the significantly increased inhibition immediately at the end of the tNIRS at the ISI of 2 ms ($t = 2.48$, $p = 0.028$) and decreased excitation at the ISI of 9 ms ($t = 3.58$, $p = 0.0037$) (**Figure 3**). There were no other significant main or interaction effects with regard to SICF/ICF.

tNIRS had no significant effect on LICI and motor-evoked recruitment curves as revealed by repeated measurements of ANOVA.

Implicit Motor Learning

Repeated measures ANOVA revealed a significant main effect on BLOCK [$F_{(7, 217)} = 22.20$, $p < 0.001$] There was no significant effect on CONDITION [$F_{(1, 31)} = 0.2$, $p = 0.66$] and the CONDITION × BLOCK interaction was also not significant [$F_{(7, 217)} = 0.43$, $p = 0.88$].

With regard to the ER, repeated measures ANOVA revealed a significant main effect on BLOCK [$F_{(7, 217)} = 17.26$ $p < 0.001$] There was no significant effect on CONDITION [$F_{(1, 31)} = 0.13$, $p = 0.72$] and the CONDITION × BLOCK interaction was also not significant [$F_{(7, 217)} = 0.53$, $p = 0.16$].

Perceptual Sensations and Side Effects during and after Stimulation

During active stimulation 100% of the subjects reported feeling a heating sensation during active and 7.7% of them during sham stimulation (significant difference between active and sham stimulation, Chi-square test $p < 0.001$) (**Table 1**). Pain and

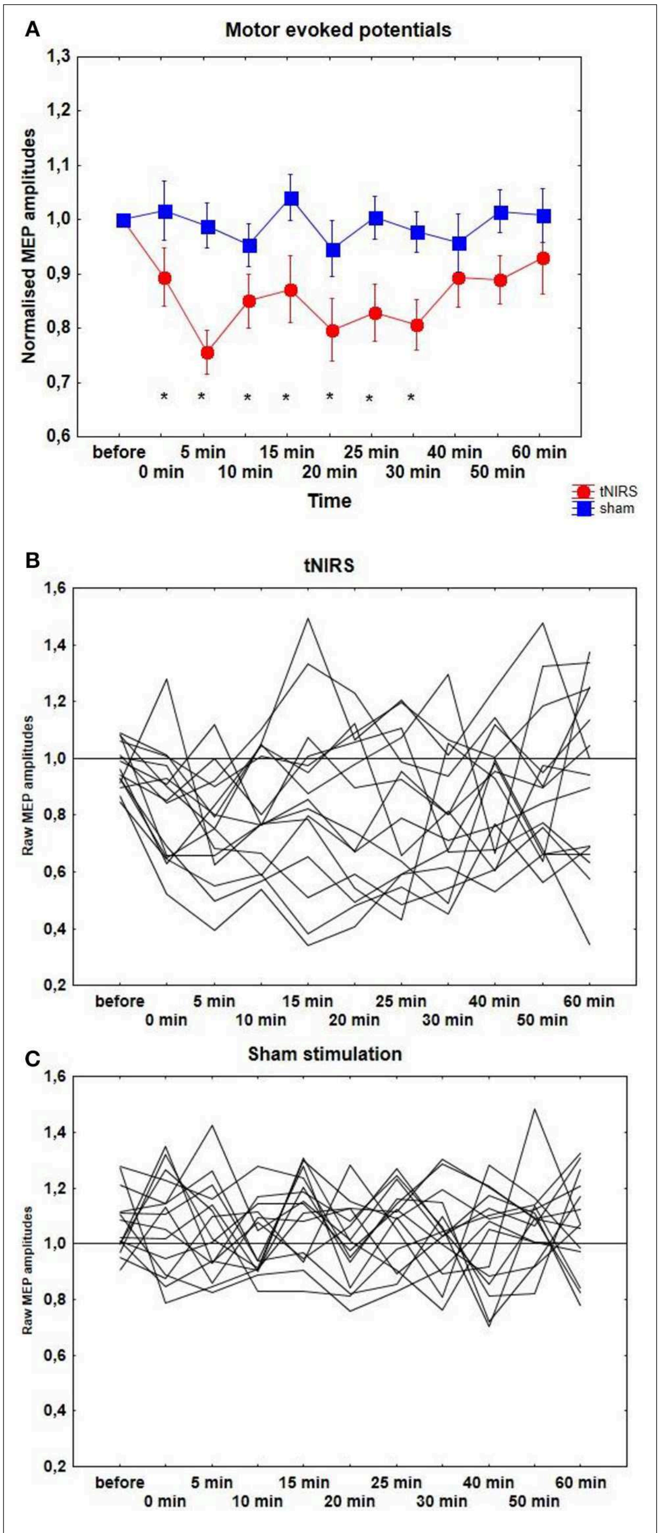


FIGURE 2 | (A) Effect of 10 min tNIRS on motor evoked potentials. Time course of motor cortex excitability changes for 60 min post-stimulation, shown after 10 min tNIRS over M1. The figure shows mean amplitudes and their SEMs. Asterisks indicate significant differences between MEP amplitudes after 0–30 min post-stimulation compared to baseline (Student's *t*-test, $p < 0.05$). **(B,C)** Individual MEP data after active and sham stimulation.

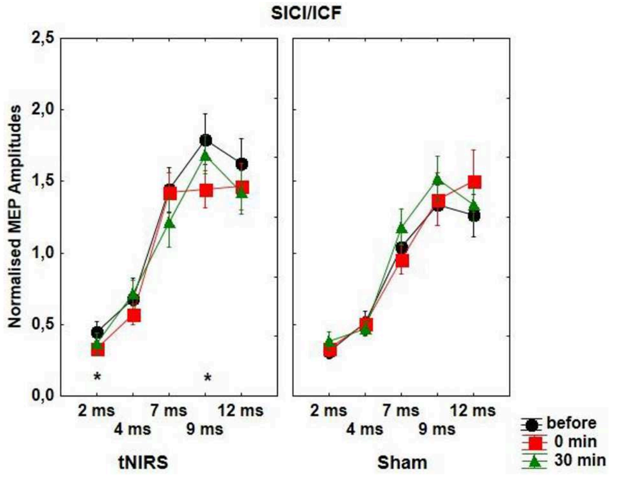


FIGURE 3 | Effect of 10 min tNIRS on SICI/ICF. The figure shows mean amplitudes and their SEMs. Asterisks indicate significant differences between MEP amplitudes after 0 min post-stimulation compared to baseline (Student' *t*-test, ISI of 2 ms; $t = 2.48$, $p = 0.028$; ISI of 9 ms; $t = 3.58$, $p = 0.0037$).

TABLE 1 | Perceptual and side effects of the stimulation.

	Tingling		Itching sensation	
	During%	**After%**	**During%**	**After%**
active	46.9	13.4	13.2	13.2
sham	7.7	7.7	0	15.4
	Heating sensation		**Pain**	
	During%	**After%**	**During%**	**After%**
active	100	26.8	60.3	26.8
sham	7.7	7.7	0	0
	Headache		**Fatigue**	
	During%	**After%**	**During%**	**After%**
active	6.6	19.8	26.8	39.6
sham	7.7	0	38.5	30.8
	Change in visual perception		**Nervousness**	
	During%	**After%**	**During%**	**After%**
active	6.6	6.6	19.8	0
sham	15.4	7.7	7.7	0

N = 15 active, 13 sham conditions.

tingling were reported by 60.3% and 46.9% of the subjects respectively (significant difference between active and sham stimulation, Chi-square test $p < 0.001$). Fatigue was higher in the sham group (38.5% vs. 26.8%) during stimulation. 66% of the subjects were able to distinguish between sham and active stimulation. After active stimulation 26.8% of the subjects experienced heating and pain sensations. Itching and tingling sensations were similar in both groups (between 7.7% and 15.4%). Light headache was reported by 19.8% of the participants.

Discussion

Earlier works using NIRS as a measurement tool, have already demonstrated that near-infrared light can penetrate the intact skull and reaches deeper tissue than red light (Chung et al., 2012). In the present study, supporting previous findings (Konstantinovic et al., 2013), we have shown that a 10 min. application of tNIRS to the M1 can inhibit cortical excitability as measured by attenuation of the amplitude of TMS-elicited MEPs. The duration of the induced inhibition was longer than the stimulation itself: the MEP amplitudes reached baseline values after 30 min poststimulation. We have further observed to an increased SICI and a decreased ICF after active stimulation. SICI reflects intracortical inhibition and is mediated by gamma aminobutyric acid ($GABA_A$) receptors, whereas ICF is most likely mediated by the glutamatergic system (Ziemann et al., 1998). Therefore, it is possible that tNIRS facilitated intracortical inhibitory networks and/or inhibited intracortical facilitatory influences of corticospinal motoneurons, by increasing GABAergic neurotransmission and/or decreasing glutamatergic actions, thus resulting in a net inhibition of MEP amplitudes. Evidence for an earlier appearance or predominance of inhibition using other transcranial stimulation methods (e.g., electrical stimulation) was already published in human (Moliadze et al., 2012) and animal studies (Le Roux et al., 2006, 2008). On the neuronal level nonlinear excitation-inhibition integration caused by shunting of excitatory synaptic currents through activated $GABA_A$ channels has been shown experimentally (Borg-Graham et al., 1998; Hao et al., 2009) and theoretically (Blomfield, 1974; Koch et al., 1983; Hao et al., 2009). Moreover, it was shown that excitatory circuits are strongly controlled by inhibitory circuits (Maffei et al., 2004). On the molecular level the reactive oxygen species (ROS)-pathway might also play a possible role in this process. Increased cellular respiration and increased oxygen consumption follow rises of intracellular ROS (Storz, 2007), which in turn, increases the overall redox potential of the cell. However, considering our stimulation duration (10 min) it can be that the products of upregulated respiration (ATP) or even the mitochondria themselves begin to downregulate and that the normally functioning GABAergic mechanisms override the already dysfacilitated excitatory circuits. It would be an important question to investigate whether these effects are due to a reduction in the activity of the mitochondria in targeted neurons.

On the behavioral level using the SRTT task we have observed no significant effect of tNIRS on the implicit learning process. This is a partly contradictory result compared to the inhibitory effect of tNIRS that we observed on the MEP amplitude. However, dissociation between MEP excitability changes and implicit learning using electrical stimulation has already been described (Antal et al., 2008; Moliadze et al., 2010). In MEP measurements and in implicit motor learning different anatomical pathways and physiological processes are involved that may reflect the involvement of diverse neuronal populations.

The study has several limitations. The most important point is, that a high percentage of participants reported cutaneous perceptions, including a heating sensation during stimulation and therefore, were able to differentiate between the active and sham stimulation conditions, which in turn, might influence the present results. In an earlier study, suppression of MEPs was observed after painful infusion of hypertonic saline into the hand muscle (Svensson et al., 2003); nevertheless, here the acute pain was induced in the muscle, from which the MEPs were recorded. Generally, positive and negative emotions (like pain) (Hajcak et al., 2007) and increased attention toward the experimental procedure (Stefan et al., 2004) have been suggested to *increase* and not to decrease MEP amplitude. Furthermore, the stimulation had an aftereffect, the MEP size reached the baseline level in ca 20 min after the end of the stimulation that is very unlikely the effect of acute local tingling and heating sensations. Finally, in our control condition, where the visual cortex was stimulated in 8 subjects, the participants experienced the same skin sensations like during M1 stimulation, however, we did not observe any MEP amplitude change. Therefore, we are convinced that the results are real and the inhibitory effect of tNIRS is due to the M1 stimulation. Nevertheless, further work should be done to develop a more appropriate placebo condition. Aside from this it is of utmost priority to minimize any accompanying cutaneous sensations.

The second point is that the individual variability with regard to the cortical excitability changes (that might be the reason of the missing effect of the stimulation in the implicit learning task) is high, although a clear tendency toward the inhibition can be observed. It is well documented that the penetration depth of infrared light depends on the thickness of the scalp and skull (e.g., Li et al., 2007; Yoshitani et al., 2007; Strangman et al., 2014) that can be very different in healthy subjects, resulting in altered penetration depths.

In summary, recent human and animal studies have shown that near-infrared light applied over the cortex may have beneficial effects on stroke rehabilitation and may minimize cognitive deficits sustained during traumatic brain injury (Hashmi et al., 2010a; Stemer et al., 2010; Ando et al., 2011). Here, we claim that tNIRS offers the potential to induce neuroplastic changes in the intact human cortex. Since tNIRS is believed to modify mitochondrial respiration, it might offer a possibility to aid in the management of a wide variety of disease pathologies originating from mitochondrial dysfunction.

Acknowledgments

We acknowledge support by the German Research Foundation and the Open Access Publication Funds of the University of Göttingen. We would like to thank Dr. G. G. Ambrus for his technical assistance, to Suhaidah Jofrry for executing the control experiments, and Alexander Opitz for the theoretical comments. We would also like to thank Dr. M. Weber of WeberMedical, GmbH for providing the stimulation equipment.

References

Ando, T., Xuan, W., Xu, T., Dai, T., Sharma, S. K., Kharkwal, G. B., et al. (2011). Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice. *PLoS ONE* 6:e26212. doi: 10.1371/journal.pone.0026212

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., and Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul.* 1, 97–105. doi: 10.1016/j.brs.2007.10.001

Bjordal, J. M., Couppe, C., Chow, R. T., Tuner, J., and Ljunggren, E. A. (2003). A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. *Aust. J. Physiother.* 49, 107–116. doi: 10.1016/S0004-9514(14)60127-6

Blomfield, S. (1974). Arithmetical operationsperformedbynerve cells. *Brain Res.* 69, 115–124. doi: 10.1016/0006-8993(74)90375-8

Borg-Graham, L. J., Monier, C., and Fregnac, Y. (1998). Visual input evokes transient and strong shunting inhibition in visual cortical neurons. *Nature* 393, 369–373. doi: 10.1038/30735

Bozkurt, A., and Onaral, B. (2004). Safety assessment of near infrared light emitting diodes for diffuse optical measurements. *Biomed. Eng. Online* 3:9. doi: 10.1186/1475-925X-3-9

Chung, H., Dai, T., Sharma, S. K., Huang, Y. Y., Carroll, J. D., and Hamblin, M. R. (2012). The nuts and bolts of low-level laser (light) therapy. *Ann. Biomed. Eng.* 40, 516–533. doi: 10.1007/s10439-011-0454-7

Detaboada, L., Ilic, S., Leichliter-Martha, S., Oron, U., Oron, A., and Streeter, J. (2006). Transcranial application of low-energy laser irradiation improves neurological deficits in rats following acute stroke. *Lasers Surg. Med.* 38, 70–73. doi: 10.1002/lsm.20256

Gigo-Benato, D., Geuna, S., and Rochkind, S. (2005). Phototherapy for enhancing peripheral nerve repair: a review of the literature. *Muscle Nerve* 31, 694–701. doi: 10.1002/mus.20305

Gur, A. Y., Lampl, Y., Gross, B., Royter, V., Shopin, L., and Bornstein, N. M. (2007). A new scale for assessing patients with vertebrobasilar stroke - the Israeli Vertebrobasilar Stroke Scale (IVBSS): Inter-rater reliability and concurrent validity. *Clin. Neurol. Neurosurg.* 109, 317–322. doi: 10.1016/j.clineuro.2006.12.008

Hajcak, G., Molnar, C., George, M. S., Bolger, K., Koola, J., and Nahas, Z. (2007). Emotion facilitates action: a transcranial magnetic stimulation study of motor cortex excitability during picture viewing. *Psychophysiology* 44, 91–97. doi: 10.1111/j.1469-8986.2006.00487.x

Hao, J., Wang, X. D., Dan, Y., Poo, M. M., and Zhang, X. H. (2009). An arithmetic rule for spatial summation of excitatory and inhibitory inputs in pyramidal neurons. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21906–21911. doi: 10.1073/pnas.0912022106

Hashmi, J. T., Huang, Y. Y., Osmani, B. Z., Sharma, S. K., Naeser, M. A., and Hamblin, M. R. (2010a). Role of low-level laser therapy in neurorehabilitation. *PM R* 2(12 Suppl. 2), S292–S305. doi: 10.1016/j.pmrj.2010.10.013

Hashmi, J. T., Huang, Y. Y., Sharma, S. K., Kurup, D. B., De Taboada, L., Carroll, J. D., et al. (2010b). Effect of pulsing in low-level light therapy. *Lasers Surg. Med.* 42, 450–466. doi: 10.1002/lsm.20950

Huang, Y. Y., Chen, A. C., Carroll, J. D., and Hamblin, M. R. (2009). Biphasic dose response in low level light therapy. *Dose Response* 7, 358–383. doi: 10.2203/dose-response.09-027.Hamblin

Iino, M. (2006). Ca2+-dependent inositol 1,4,5-trisphosphate and nitric oxide signaling in cerebellar neurons. *J. Pharmacol. Sci.* 100, 538–544. doi: 10.1254/jphs.CPJ06006X

Ilic, S., Leichliter, S., Streeter, J., Oron, A., DeTaboada, L., and Oron, U. (2006). Effects of power densities, continuous and pulse frequencies, and number of sessions of low-level laser therapy on intact rat brain. *Photomed. Laser Surg.* 24, 458–466. doi: 10.1089/pho.2006.24.458

Karu, I. (1987). Photobiological fundamentals of low-power laser therapy. *IEEE J. Quantum Electron* 23, 1703–1717. doi: 10.1109/JQE.1987.1073236

Karu, T. (1989). Laser biostimulation: a photobiological phenomenon. *J. Photochem. Photobiol. B Biol.* 3, 638–640. doi: 10.1016/1011-1344(89)80088-0

Karu, T. (1999). Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J. Photochem. Photobiol. B. Biol.* 49, 1–17. doi: 10.1016/S1011-1344(98)00219-X

Koch, C., Poggio, T., and Torre, V. (1983). Nonlinear interactions in a dendritic tree: Localization, timing, and role in information processing. *Proc. Natl. Acad. Sci. U.S.A.* 80, 2799–2802. doi: 10.1073/pnas.80.9.2799

Konstantinovic, L. M., Jelic, M. B., Jeremic, A., Stevanovic, V. B., Milanovic, S. D., and Filipovic, S. R. (2013). Transcranial application of near-infrared low-level laser can modulate cortical excitability. *Lasers Surg. Med.* 45, 648–653. doi: 10.1002/lsm.22190

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *J. Physiol.* 471, 501–519. doi: 10.1113/jphysiol.1993.sp019912

Lampl, Y., Zivin, J. A., Fisher, M., Lew, R., Welin, L., Dahlof, B., et al. (2007). Infrared laser therapy for ischemic stroke: a new treatment strategy results of the NeuroThera effectiveness and Safety Trial-1 (NEST-1). *Stroke* 38, 1843–1849. doi: 10.1161/STROKEAHA.106.478230

Le Roux, N., Amar, M., Baux, G., and Fossier, P. (2006). Homeostatic control of the excitation-inhibition balance in cortical layer 5 pyramidal neurons. *Eur. J. Neurosci.* 24, 3507–3518. doi: 10.1111/j.1460-9568.2006.05203.x

Le Roux, N., Amar, M., Moreau, A., Baux, G., and Fossier, P. (2008). Impaired GABAergic transmission disrupts normal homeostatic plasticity in rat cortical networks. *Eur. J. Neurosci.* 27, 3244–3256. doi: 10.1111/j.1460-9568.2008.06288.x

Li, H., Ruan, J., Xie, Z., Wang, H., and Liu, W. (2007). Investigation of the critical geometric characteristics of living human skulls utilising medical image analysis techniques. *Int. J. Veh. Saf.* 2, 345–367. doi: 10.1504/IJVS.2007.016747

Litscher, D., and Litscher, G. (2013). Laser therapy and stroke: quantification of methodological requirements in consideration of yellow laser. *Int. J. Photoenergy* 2013:575798. doi: 10.1155/2013/575798

Litscher, G., Liu, C. Z., Wang, L., Wang, L. P., Li, Q. Q., Shi, G. X., et al. (2013). Improvement of the dynamic responses of heart rate variability patterns after needle and laser acupuncture treatment in patients with burnout syndrome: a transcontinental comparative study. *Evid. Based Complement. Alternat. Med.* 2013:128721. doi: 10.1155/2013/128721

Maffei, A., Nelson, S. B., and Turrigiano, G. G. (2004). Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nat. Neurosci.* 7, 1353–1359. doi: 10.1038/nn1351

Moliadze, V., Antal, A., and Paulus, W. (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. *J. Physiol.* 588(Pt 24), 4891–4904. doi: 10.1113/jphysiol.2010.196998

Moliadze, V., Atalay, D., Antal, A., and Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul.* 5, 505–511. doi: 10.1016/j.brs.2011.11.004

Naeser, M. A., and Hamblin, M. R. (2011). Potential for transcranial laser or LED therapy to treat stroke, traumatic brain injury, and neurodegenerative disease. *Photomed. Laser Surg.* 29, 443–446. doi: 10.1089/pho.2011.9908

Naeser, M. A., Saltmarche, A., Krengel, M. H., Hamblin, M. R., and Knight, J. A. (2011). Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. *Photomed. Laser Surg.* 29, 351–358. doi: 10.1089/pho.2010.2814

Nissen, M. J., and Bullmer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cogn. Psychol.* 19, 1–32 doi: 10.1016/0010-0285(87)90002-8

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., et al. (2003). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J. Cogn. Neurosci.* 15, 619–626. doi: 10.1162/089892903321662994

Oron, A., Oron, U., Chen, J., Eilam, A., Zhang, C., Sadeh, M., et al. (2006). Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. *Stroke* 37, 2620–2624. doi: 10.1161/01.STR.0000242775.14642.b8

Oron, A., Oron, U., Streeter, J., De Taboada, L., Alexandrovich, A., Trembovler, V., et al. (2012). Near infrared transcranial laser therapy applied at various modes to mice following traumatic brain injury significantly reduces long-term neurological deficits. *J. Neurotrauma* 29, 401–407. doi: 10.1089/neu.2011.2062

Pascual-Leone, A., Grafman, J., and Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science* 263, 1287–1289. doi: 10.1126/science.8122113

Rothwell, J. C. (1999). Paired-pulse investigations of short-latency intracortical facilitation using TMS in humans. *Electroencephalogr. Clin. Neurophysiol. Suppl.* 51, 113–119.

Schiffer, F., Johnston, A. L., Ravichandran, C., Polcari, A., Teicher, M. H., Webb, R. H., et al. (2009). Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. *Behav. Brain Funct.* 5:46. doi: 10.1186/1744-9081-5-46

Sommer, A. P., Bieschke, J., Friedrich, R. P., Zhu, D., Wanker, E. E., Fecht, H. J., et al. (2012). 670 nm laser light and EGCG complementarily reduce amyloid-beta aggregates in human neuroblastoma cells: basis for treatment of Alzheimer's disease? *Photomed. Laser Surg.* 30, 54–60. doi: 10.1089/pho.2011.3073

Stefan, K., Wycislo, M., and Classen, J. (2004). Modulation of associative human motor cortical plasticity by attention. *J. Neurophysiol.* 92, 66–72. doi: 10.1152/jn.00383.2003

Stemer, A. B., Huisa, B. N., and Zivin, J. A. (2010). The evolution of transcranial laser therapy for acute ischemic stroke, including a pooled analysis of NEST-1 and NEST-2. *Curr. Cardiol. Rep.* 12, 29–33. doi: 10.1007/s11886-009-0071-3

Storz, P. (2007). Mitochondrial ROS–radical detoxification, mediated by protein kinase D. *Trends Cell Biol.* 17, 13–18. doi: 10.1016/j.tcb.2006.11.003

Strangman, G. E., Zhang, Q., and Li, Z. (2014). Scalp and skull influence on near infrared photon propagation in the Colin27 brain template. *Neuroimage* 85, 136–149. doi: 10.1016/j.neuroimage.2013.04.090

Svensson, P., Miles, T. S., McKay, D., and Ridding, M. C. (2003). Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. *Eur. J. Pain* 7, 55–62. doi: 10.1016/S1090-3801(02)00050-2

Valls-Sole, J., Pascual-Leone, A., Wassermann, E. M., and Hallett, M. (1992). Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr. Clin. Neurophysiol.* 85, 355–364. doi: 10.1016/0168-5597(92)90048-G

Villringer, A., Planck, J., Hock, C., Schleinkofer, L., and Dirnagl, U. (1993). Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci. Lett.* 154, 101–104. doi: 10.1016/0304-3940(93)90181-J

Yoshitani, K., Kawaguchi, M., Miura, N., Okuno, T., Kanoda, T., Ohnishi, Y., et al. (2007). Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. *Anesthesiology* 106, 458–462. doi: 10.1097/00000542-200703000-00009

Ziemann, U., Tergau, F., Wischer, S., Hildebrandt, J., and Paulus, W. (1998). Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. *Electroencephalogr. Clin. Neurophysiol.* 109, 321–330. doi: 10.1016/S0924-980X(98)00023-X

Zivin, J. A., Sehra, R., Shoshoo, A., Albers, G. W., Bornstein, N. M., Dahlof, B., et al. (2014). NeuroThera® Efficacy and Safety Trial - 3 (NEST-3): a double-blind, randomized, sham-controlled, parallel group, multicenter, pivotal study to assess the safety and efficacy of transcranial laser therapy with the NeuroThera® Laser System for the treatment of acute ischemic stroke within 24 h of stroke onset. *Int. J. Stroke* 9, 950–955. doi: 10.1111/j.1747-4949.2012.00896.x

Conflict of Interest Statement: The study was partially supported by WeberMedical, GmbH. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 24 June 2016
doi: 10.3389/fnbeh.2016.00135

Cognitive and Neurophysiological Effects of Non-invasive Brain Stimulation in Stroke Patients after Motor Rehabilitation

***Federico D'Agata*[1]*, Elena Peila*[1]*, Alessandro Cicerale*[1]*, Marcella M. Caglio*[1]*, Paola Caroppo*[1,2]*, Sergio Vighetti*[1]*, Alessandro Piedimonte*[1]*, Alice Minuto*[3]*, Marcello Campagnoli*[3]*, Adriana Salatino*[4]*, Maria T. Molo*[4]*, Paolo Mortara*[1]*, Lorenzo Pinessi*[1] *and Giuseppe Massazza*[3]**

[1] Department of Neuroscience, University of Turin, Turin, Italy, [2] UO Neurology V - Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, [3] Physical Medicine and Rehabilitation, University of Turin, Turin, Italy, [4] Molo ONLUS, Turin, Italy

The primary aim of this study was to evaluate and compare the effectiveness of two specific Non-Invasive Brain Stimulation (NIBS) paradigms, the repetitive Transcranial Magnetic Stimulation (rTMS), and transcranial Direct Current Stimulation (tDCS), in the upper limb rehabilitation of patients with stroke. Short and long term outcomes (after 3 and 6 months, respectively) were evaluated. We measured, at multiple time points, the manual dexterity using a validated clinical scale (ARAT), electroencephalography auditory event related potentials, and neuropsychological performances in patients with chronic stroke of middle severity. Thirty four patients were enrolled and randomized. The intervention group was treated with a NIBS protocol longer than usual, applying a second cycle of stimulation, after a washout period, using different techniques in the two cycles (rTMS/tDCS). We compared the results with a control group treated with sham stimulation. We split the data analysis into three studies. In this first study we examined if a cumulative effect was clinically visible. In the second study we compared the effects of the two techniques. In the third study we explored if patients with minor cognitive impairment have most benefit from the treatment and if cognitive and motor outcomes were correlated. We found that the impairment in some cognitive domains cannot be considered an exclusion criterion for rehabilitation with NIBS. ERP improved, related to cognitive and attentional processes after stimulation on the motor cortex, but transitorily. This effect could be linked to the restoration of hemispheric balance or by the effects of distant connections. In our study the effects of the two NIBS were comparable, with some advantages using tDCS vs. rTMS in stroke rehabilitation. Finally we found that more than one cycle (2–4 weeks), spaced out by washout periods, should be used, only in responder patients, to obtain clinical relevant results.

Keywords: non-invasive brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, mirror-box therapy, stroke rehabilitation

OPEN ACCESS

Edited by:
Nuno Sousa,
University of Minho, Portugal

Reviewed by:
Leonardo G. Cohen,
National Institutes of Health (NIH), USA
Ander Ramos-Murguialday,
University of Tübingen, Germany

****Correspondence:***
Federico D'Agata
federico.dagata@unito.it

Received: *25 April 2015*
Accepted: *13 June 2016*
Published: *24 June 2016*

Citation:
D'Agata F, Peila E, Cicerale A, Caglio MM, Caroppo P, Vighetti S, Piedimonte A, Minuto A, Campagnoli M, Salatino A, Molo MT, Mortara P, Pinessi L and Massazza G (2016) Cognitive and Neurophysiological Effects of Non-invasive Brain Stimulation in Stroke Patients after Motor Rehabilitation. Front. Behav. Neurosci. 10:135. doi: 10.3389/fnbeh.2016.00135

INTRODUCTION

Motor and cognitive impairment are frequent aftermaths of brain damage after a stroke. Many authors reports cognitive deficits in 12–56% of stroke patients and reduced performances in several cognitive domains in 32% (Ebrahim et al., 1985; Tatemichi et al., 1994; Patel et al., 2002). Moreover, dysfunctions in the use of upper limb and in functional walking are among the more common consequences for many stroke survivors. Of note, only 5% of adult stroke survivors regain full function of the upper limb and 20% do not recover any functional use.

The severity of cognitive impairment negatively correlates with motor and functional recovery achieved in stroke patients after rehabilitation. Indeed, a cognitive assessment should be used to select patients that could have the best benefits from rehabilitation (Patel et al., 2002; Mehta et al., 2003; Saxena et al., 2007; Rabadi et al., 2008).

Event Related Potentials (ERP) are a reproducible electrophysiological response to an external stimulus (visual or auditory), representing the brain activity associated with various cognitive processes such as selective attention, memory, or decision making. Interestingly, ERP can be valuable in the diagnosis of cognitive impairment and are able to track the cognitive changes during the follow-up in stroke patients (Trinka et al., 2000; Alonso-Prieto et al., 2002; Yamagata et al., 2004; Stahlhut et al., 2014).

Recently, Non-Invasive Brain Stimulation (NIBS) techniques have been proposed as support of standard cognitive and motor rehabilitation. The application of NIBS in stroke rehabilitation arises from the observation that cortical excitability can be modulated after electrical or magnetic brain stimulation. It can be reduced or enhanced (Miniussi et al., 2008; Sandrini and Cohen, 2013) depending on many factors (stimulation parameters, type of stimulation technique, timing of the stimulation, brain target region, and state of mind).

The physiological mechanisms underlying brain stimulation effects are still partially unknown, but several evidences explain these effects with Long Term Potentiation (LTP) and Long Term Depression (LTD) like mechanisms (Thickbroom, 2007; Fritsch et al., 2010; Bliss and Cooke, 2011).

Repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) are the most used NIBS techniques in rehabilitation (Hummel et al., 2005; Miniussi et al., 2008; Bolognini et al., 2009). Both can induce long lasting effect on cortical plasticity (30–90 min). Modification of cortical activity may improve the subject's ability to relearn or acquire new strategies for carrying out motor or behavioral task, by facilitating perilesional activity or by suppressing maladaptive interfering activity from other brain areas (Miniussi et al., 2008). Even if most of the effects are transient, NIBS during or before a learning process may yield the behavioral improvements more robust and stable (Rossi and Rossini, 2004; Pascual-Leone, 2006). Indeed, during motor learning not only the fast (intra-sessions) and slow (inter-sessions) learning during training are relevant, but also the memory consolidation and the savings (Wessel et al., 2015). Plasticity induced by NIBS could thus have important effects not only in the online phase of motor rehabilitation, but also in the offline phases.

A growing number of studies indicates that NIBS could be useful in chronic stroke rehabilitation (Hummel and Cohen, 2006; Sandrini and Cohen, 2013; Liew et al., 2014; Wessel et al., 2015), but no one compared directly the two techniques or explored the link between cognitive and motor improvement. TMS is able to directly induce action potentials in the axons while the currents used in tDCS (1–2 mA) cannot. The first technique is, therefore, best suited to be used offline, while the second can be used online in conjunction with other rehabilitation techniques or tasks (Wessel et al., 2015). Simis et al. (2013) compared rTMS and tDCS in healthy subjects, observing that both techniques induced similar motor gains. The comparison of brain plasticity induced by NIBS in pathologic subjects could thus extend significantly the Simis' results.

In this paper, the primary aim was to evaluate and compare the motor and cognitive changes induced by rTMS and tDCS in the upper limb rehabilitation in patients with stroke, both in short and in long term outcome. Secondarily we searched for a possible link between motor and cognitive measures.

We chose the most effective paradigm of rTMS in chronic stroke according to meta-analyses and consensus papers (Lefaucheur et al., 2014), a low-frequency protocol applied onto the controlesional motor cortex (M1). For tDCS, in the absence of a gold standard, we chose a paradigm with a dual sites montage validated in non-inferiority trials (Schlaug et al., 2008; Lüdemann-Podubecká et al., 2014). The tDCS was performed in conjunction with a cognitive training focused on the brain representation of the hands, the mirror-box therapy (MT), to direct the neuromodulation effect as wished. Our aim was to create a paradigm easy to apply in a clinical setting.

To compare the NIBS techniques in the same patients we created a treatment longer than usual applying a second cycle of stimulation, after a washout period, using different techniques in the two cycles (rTMS/tDCS).

A randomized clinical trial divided into three studies was designed to explore the following issues:

A longer NIBS stimulation could be beneficial in stroke rehabilitation?
What are the differences between rTMS and tDCS in stroke rehabilitation?
NIBS motor stimulation effects can modulate or be modulated by patients' cognitive status?

In the first study we evaluated if a cumulative effect, mediated by an offline improvement (consolidation or savings), was clinically detectable. We also evaluated the differences between a first priming cycle with rTMS followed by tDCS and first priming with tDCS followed by rTMS.

In the second study we compared the effects of the two techniques to test if brain plasticity effects could depend on the type of NIBS. In the third study, we searched for a possible link between motor and cognition changes, evaluating if cognitive measures changed in patients with motor improvement differently from the patients without motor improvement.

MATERIALS AND METHODS

Patients

Thirty four consecutive patients (see **Table 1** for demographic and clinical data), with chronic ischemic or hemorrhagic stroke (>6 months from the accident), aged between 18 and 70 years, attending the Physical Medicine and Rehabilitation department at AOU Città della Salute e della Scienza—Presidio Molinette Hospital in Torino, Italy, were enrolled in the study. Exclusion criteria were: global cognitive impairment (Mini Mental State Examination < 25), severe functional disability (Barthel Index < 45), severe psychiatric disorders, degenerative neurological disorders, epilepsy, and severe medical conditions. Patients with implanted drug infusion systems, spinal/brain-stimulators, or endovascular coils were excluded. In accordance with institutional guidelines and the Declaration of Helsinki, the local ethics committee gave approval to this study and all the involved participants signed informed written consent. The study was registered on ClinicalTrials.gov, identifier: NCT02525393. We selected a sample size similar to the numbers usually used in literature (about 31 subjects for rTMS and 30 for tDCS, means estimated from Pollock et al., 2014).

Experimental Design

The trial was randomized double blind (Subject, Caregiver, Outcomes Assessor), interventional, with a factorial design (see **Figure 1**). Patients were randomly assigned to 3 arms:

The first intervention group (rTMS+tDCS, $N = 16$) received 10 daily sessions of rTMS for 2 weeks and after a washout period (at least 6 months) 10 daily sessions of dual-tDCS + MT for 2 weeks.

The second intervention group (tDCS+rTMS, $N = 8$) received dual-tDCS + MT and then rTMS, after washout.

A control group ($N = 10$) received 10 daily sessions of sham-tDCS + MT for 2 weeks.

The primary outcome measure was the Action Research Arm Test (ARAT) a quantitative upper extremity function test. The endpoint for a successful intervention was set, considering the Minimal Clinically Important Difference (MCID/MCD), in a range between 3.5 and 5.7 points (Van der Lee et al., 2001; Lin et al., 2009).

The secondary outcome measures were cognitive functions evaluated by electroencephalography (EEG) auditory evoked response potentials (ERP) and neuropsychological paper and pencil tests (NPS).

Time frames for the outcome measurements and interventions administration are shown in **Figure 1**.

Interventions were administered at weeks 2–3 and at around weeks 26–27 (6 months and 2–3 weeks). At baseline (T0) ARAT, ERP and NPS were assessed, at T1 (4 weeks) ARAT, ERP and NPS, at T2 (3 months) ARAT, at T3 (6 months) ARAT and NPS, at T0′ (6–11 months and 1 week) ARAT, ERP and NPS, at T1′ (7–12 months) ARAT, ERP and NPS, at T2′ (9–14 months) ARAT, at T3′ (12–17 months) ARAT and NPS.

The study was realized in a clinical setting so we decide to apply both stimulations (rTMS, tDCS) in the same patients to compare the safety and effectiveness of the techniques intra-patient, overcoming the problem of the sample's heterogeneity.

TABLE 1 | Clinical and demographic data.

Variable	Intervention	Sham	p*
N	24	10	–
Age [years]	57 (12)	65 (12)	0.079
Gender M/F (%)	67/33%	70/30%	0.999
Education [years]	10 (4)	10 (4)	0.869
Affected hemisphere R/L (%)	50/50%	40/60%	0.715
Etiopathogenesis (%)			0.999
Ischemic	71%	70%	
Hemorrhagic	29%	30%	
Previous stroke events (%)	21%	30%	0.666
Lesion localization (%)			0.735
Cortical	25%	10%	
Subcortical	62%	80%	
Both	13%	10%	
Time from stroke [mos]	41 (39)	37 (32)	0.797
Smoke (%)	25%	10%	0.644
Hypertension (%)	72%	70%	0.999
Diabetes (%)	8%	30%	0.138
Dyslipidemia (%)	38%	40%	0.999
Stroke familiar history (%)	21%	30%	0.666
THERAPY			
Antidepressant	71%	40%	0.130
Antihypertensive	58%	60%	0.999
Antiplatelet	79%	70%	0.666
NIBS SEQUENCE			
TMS-tDCS	8	–	–
tDCS-TMS	16		
SIDE EFFECTS IN 10 SESSIONS**			
TMS	4		–
tDCS	6	3	
Drop outs (%)	24%	0%	–

*Mean and (standard deviation) or frequency, *p, probability for two sample independent t-test or Kruscal–Wallis or Fisher's exact test. **tiredness or headache for sham, tDCS and TMS, transient hearing loss for TMS.*

Demographic or clinical variables did not significantly differ between the patients that received the interventions and the control group (see **Table 1**).

Action Research Arm Test

The ARAT is a quantitative scale with 19 tasks graded from 0 to 3 (0 = cannot execute the task, 3 = can perform normally). It has four subscales: grasp (6 tasks), grip (4 tasks), pinch (6 tasks), and gross movements (3 tasks). In the first three subscales the tasks consist in grasping, moving and releasing different objects (e.g., wood block, glass, tube, ball), the last scale consists of three large movements (i.e., place hand behind the head, place hand on the top of the head, and move hand to mouth). Summing the scores, ARAT ranges from 0 to 57; higher scores indicate better upper extremity functionality. It is a reliable, valid, and standardized functional assessment tool with good to excellent psychometric characteristics (Van der

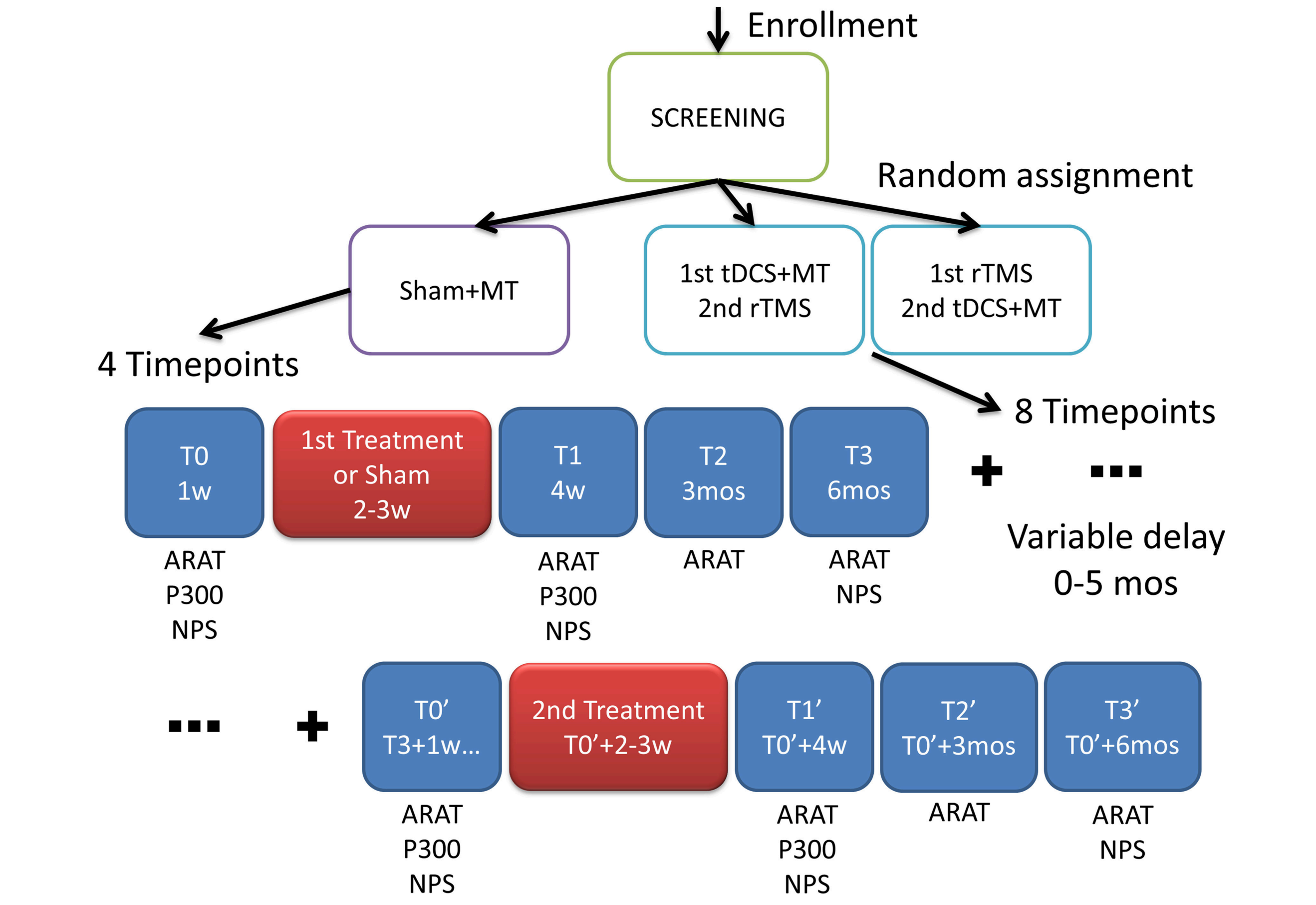


FIGURE 1 | Experimental design. After screening the patients were randomized into three groups with different interventions: MT, Mirror Therapy; tDCS, transcranial Direct Current Stimulation; rTMS, repetitive Transranial Magnetic Stimulation. In the scheme the outcome measures: ARAT, Action Research Arm Test; P300, cognitive auditory evoked response potentials; NPS, neuropsychological test where assessed in multiple time frames; w, week; mos, months.

Lee et al., 2001; Connell and Tyson, 2012; Pandian and Arya, 2014).

Event Related Potentials

Electroencephalography data were recorded using a 20 channel EEG Galileo Star System (Esaote Biomedica, Verona). The patient was placed in a comfortable seated position, controlled by a technician in order to prevent drowsiness and limb movements. Nineteen standard scalp electrodes were applied to the scalp in accordance with the 10–20 International System (Fz, F1, F2, F3, F4, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2). Impedance was <2 kΩ in each active lead before the starting of the recording, and the reference was obtained by averaging the channels. Data were collected for each subject and digitized at a sampling rate of 256 Hz, with a band pass filter of 0.1–70 Hz and a notch filter to remove the main electrical noise in each channel. EEG was recorded for 5 min periods at rest (baseline). Electrooculography was simultaneously recorded with two electrodes placed near the left eye to detect and reject ocular movement artifacts from EEG data offline. ERP was recorded using the auditory oddball paradigm. The subjects were asked to react by counting target stimuli appearing rarely (r) amongst a series of more common stimuli (f) administered bilaterally by stereophonic earphones at 100 dB. Rare stimuli consisted in a 1500 Hz pure tone and frequent stimuli consisted in a 1000 Hz pure tone, presented in random order and with a mean r/f ratio of 1 r every 6 f. The recorded signal was cut appropriately (the time window started 200 ms before and ended 1100 ms after the stimulus) and ERP were averaged separately for the rare and frequent stimulus (using a mean of 20 stimuli), and the latencies of endogenous N200 and P300 components were evaluated according to the international recommendation (Goodin et al., 1994).

Neuropsychological Assessment

The patients were evaluated by a standardized neuropsychological assessment consisting of a battery of cognitive tests (described below) involving the following domains: verbal short-term memory, visuospatial learning, working memory, verbal learning, attention and frontal executive functions, and general cognitive impairment. Parallel and equivalent forms were used for all tests; we used standardized tests with normative values for the Italian population (Spinnler and Tognoni, 1987).

Mini Mental State Examination (MMSE)

This test is the most widely used, single measure of global cognitive functioning. It is a screening tool and it is utilized in evaluating mental state in research and clinical practice, testing global cognitive impairment.

Forward and Backward Digit Span

The participant has to remember lists of increasing length of single-digit numbers and recalls them in the right and in the opposite order. Performance is defined by the longest sequence at which participants correctly recall at least two out of three sequences. This test is a measure of mental tracking as well as brief storage and mental manipulation.

Attentional Matrices

It is used to evaluate attentional functions, in particular selective and sustained attention. Three matrices of numbers are administered with the instruction to cross out as fast as possible target numbers of either one, two, or three digits. The purpose of this test is to assess the subjects' ability to detect visual targets among distractors.

Short Story Test

This test assesses verbal memory function; the experimenter reads a short story only once and then the examinees should recall as much as they can immediately upon finishing. After 10 min have passed the examinee should repeat the recall.

Copy of Figure

This test is used to assess visuospatial and visuoconstructive skills, visual memory, and executive functioning. The examinees are asked to reproduce a drawing, first by copying it freehand, and then drawing from memory.

Visual Search and Cancellation Tasks

The number of items omitted is an indication of vigilance and the proportion of items omitted in each quadrant of the test page can suggest the presence of a possible unilateral spatial neglect.

Nelson MCST

This test is an abbreviated and Modified version of the Wisconsin Card Sorting Test; it assesses many aspects of executive functioning including mental flexibility and concept formation.

Hamilton Depression Rating Scale (HDRS)

It is the most widely used clinician-administered depression assessment scale. A limitation of the HDRS is that atypical symptoms of depression are not assessed (Hamilton, 1980).

Stimulation Protocols

The main target of the stimulation protocols was to normalize the inter-hemispheric inhibition that is generally altered in stroke patients (Wessel et al., 2015). It has been demonstrated that anodal tDCS/high frequency rTMS applied to ipsilesional M1 and cathodal tDCS/low frequency applied to contralesional M1 can improved motor functions of the affected upper limb in chronic stroke patients (Sandrini and Cohen, 2013; Liew et al., 2014; Wessel et al., 2015).

Inhibitory low frequency rTMS (1 Hz) was administrated using a PowerMAG 100 device (MAG&More, München), at 80% resting motor threshold, for 15 min (900 stimuli) over the intact M1 with an eight-shaped coil. The coil was placed on M1, aiming for cortical area coding for hands' movement.

Single pulse TMS was used to determine bilateral M1 hot spots for the first dorsal interosseus (FDI) muscles defined as the place onto the scalps where the motor evoked potential (MEP) was maximum. MEP where obtained with the 120% of the minimum intensity required eliciting electromyography activity of at least 50 μV peak-to-peak amplitude in $\geq$50% of pursued trials ($\geq$3/6) with the muscle at rest.

We registered surface electromyography with the Neurowerk EMG (Sigma Medizin–Technik, Gelenau/Erzgebirge) moving the coil in a grid of 0.5-cm steps medial, lateral, posterior, and anterior until the point of the maximum MEP was ascertained. The procedure was repeated iteratively until the hot spot was identified. The distances between C3/C4 and TMS hotspots were noted bilaterally for all patients. Cortical targets were identified using SofTaxic neuronavigation system (EMS, Bologna) along sessions.

tDCS was administrated using a HDC Stim device (Newronica, Milan), via two $5 \times 5\,cm^2$ pads (one anode and one cathode) soaked with saline solution. The tDCS was applied with the cathode onto the controlesional M1 and the anode onto the perilesional M1, the stimulation was online together with mirror-box therapy (MT). The anode (stimulating activity) was placed on the damaged hemisphere in the area corresponding to C3 or C4 position in the 10–20 systems, while the cathode (inhibitory activity) was placed in the analog position on the opposite hemisphere in a dual-tDCS design. The intensity of the stimulation was set at 1.5 mA and the duration of the tDCS was set at 20 min.

In our sample the mean distance between hotspots and C3/C4 was 2.1 ± 1.7 cm for the unaffected hemisphere and 2.4 ± 1.5 cm for the lesioned hemisphere; around 67% of the hotspots were inside the areas covered by pads.

Mirror Box Therapy

MT consisted in the optical illusion of bimanual movements created by a box with a mirror in the middle, it has been ideated by Ramachandran et al. (1995) to treat phantom limb pain and has also been widely used as a rehabilitation tool after stroke (Dohle et al., 2009).

The box consisted in a wooden enclosure separated in two sections by a mirror. The patients had to insert his/her hand through the holes situated on the side of the box and could watch the normal hand while performing the requested gestures. The sensation of the movement of the plegic hand was generated when the patients looked at the reflection of the normal hand during the exercises. During the tDCS application the patient had to execute 3 series of 25 repetitions of 6 different movements (e.g., the hitcher gesture). The exercises were changed completely between the first and the second week of intervention.

Only tDCS stimulation was paired with MT to enhance its specificity to reach the level of focal rTMS targeting the hand area. In fact, one way to gain specificity is to have a precise simulation of the delivered power on a small anatomical area of interest (e.g., HD-tDCS; Bikson et al., 2013), but a simpler way is the activity-selectivity technique. tDCS will preferentially modulate specific forms of ongoing activity, so we paired it with an online task focused on hand movement to boost specifically ongoing plasticity activated by the task (Bikson et al., 2013).

Statistical Analysis

We adopted parametric statistics (*t*-test, ANOVA) when needed, otherwise we adopted non parametric tests (χ^2 or Fisher's Exact test, Kruskal–Wallis's H, Friedman's test). For *post-hoc* comparisons we used Tukey HSD or Simes corrections (respectively for parametric and non-parametric tests).

The differences between groups at baseline for clinical, demographic, or outcome measures were tested.

As we tested multiple hypotheses with three different studies we also controlled if the significative results ($p < 0.05$) are still significant after a Bonferroni correction ($p < 0.017$) for multiple comparisons.

Study 1—Clinically Efficacy and Safety of Two Cycles of NIBS

To compare the efficacy of the treatment vs. sham for the ARAT outcome we used the repeated measures ANOVA (4 time frames: baseline, after interventions, short, and long follow-up) and one between factor (3 levels: tDCS+MT+rTMS, rTMS+tDCS+MT, sham+MT). In addition, we compared, with the same model, the sham group and the subgroup of responders, defined as patients that get an improvement in ARAT score after the first stimulation, to look if responders reached the MCID/MCD. Finally, we used a repeated measures ANOVA (8 time frames: baseline, after one cycle of NIBS, short and long follow-up, after pause, after second cycle of NIBS, second short and long follow-up) and one between factor (priming stimulation tDCS or rTMS) to look if the second cycle could be useful and if the order of priming stimulation was relevant on outcome.

Similar model were used for ERP and NPS with appropriate repetitions over time frames.

To compare ERP we used the repeated measures ANOVA (2 time frames: baseline and after interventions and 10 electrodes: F3, F4, F7, F8, C3, C4, P3, P4, T3, T4) and one between factor (3 levels: tDCS+MT+rTMS, rTMS+tDCS+MT, sham+MT). In addition, we used the repeated measures ANOVA (4 time frames: baseline, after one cycle of NIBS, after pause, after second cycle of NIBS) and one between factor (priming stimulation tDCS or rTMS).

To compare NPS we used the repeated measures ANOVA (3 time frames: baseline, after interventions and 6 months follow-up) and one between factor (3 levels: tDCS+MT+rTMS, rTMS+tDCS+MT, sham+MT). In addition, we used the repeated measures ANOVA (6 time frames: baseline, after one cycle of NIBS, long follow-up after pause, after second cycle of NIBS, second long-follow-up) and one between factor (priming stimulation tDCS or rTMS).

Study 2—Comparison of tDCS and rTMS Clinical Efficacy

To compare tDCS and rTMS induced changes for ARAT, ERP, and NPS intra-patients in the real stimulations groups we used a repeated measures ANOVA with time (4, 2, or 3 levels for ARAT, ERP, and NPS, respectively) and type of NIBS (two levels) as factors.

We also tested if rTMS and tDCS had a similar level of specificity looking at the profiles of ARAT subscales that, in our hypothesis, should be improved in a similar way by the two stimulations.

Study 3—Cognitive Differences in Patients That Responded to Motor Rehabilitation

We also looked if responders had some differences in the cognitive measures (ERP and NPS) at baseline or after one or after two cycles of stimulations using repeated measure ANOVA with time (3 levels, within) and responders vs. no-responders (between) as factors.

RESULTS

Patients

ARAT did not differ at baseline ($p = 0.212$).

At baseline, there were significant differences for the N200 and P300 in the study group. Indeed the sham group had shorter latencies compared to other groups (grand mean: N200 $F = 9.1$, $p = 0.001$ *post-hoc* sham < rTMS+tDCS, tDCS+rTMS; P300 $F = 10.1$, $p < 0.001$ *post-hoc* sham < rTMS+tDCS, tDCS+rTMS). Considering the P300 grand mean, latencies were over a normative cut off, determined on the basis of published data (Dinteren et al., 2014), without significant difference among groups (sham = 10%, rTMS+tDCS = 33%, tDCS+rTMS = 33%, Fisher = 2.0, $p = 0.498$).

Neuropsychological score did not differ between groups (**Table 2**). The total sample did not have general severe cognitive impairment (MMSE % patients Under normative Cut Off, UCO = 0%), but presented several focal deficits in many domains, especially in speed processing, attention and visuospatial skills (UCO 26–51%, **Table 2**).

Study 1—Clinically Efficacy and Safety of Two Cycles of NIBS

We did not find any significant effect on ARAT scores for time ($F = 0.7$, $p = 0.523$), group ($F = 1.1$, $p = 0.355$) or their interaction ($F = 2.2$, $p = 0.153$).

The responders subgroup included the 44% of the treated patients, while only 20% of sham patients improved their ARAT score; all responders improved also after the second intervention and the gains were stable in the 75% of cases after 6 months. Most (90%) non-responders did not improve after the second intervention. When comparing responders vs. sham (**Figure 2**), ARAT showed a significant effects for time ($F = 4.1$, $p = 0.012$, $\eta^2 = 0.2$) and time by group ($F = 3.9$, $p = 0.015$, $\eta^2 = 0.2$), but not for group ($F = 0.4$, $p = 0.531$). It is evident that the effect of time and the interaction is due to the responders that reached

TABLE 2 | Neuropsychological scores.

Test	Sham	rTMS+tDCS	tDCS+rTMS	*p**	UCO**
MMSE	28.1	26.1	27.5	0.572	0
Digit span (Forward)	5.70	4.63	5.00	0.074	15%
Digit span (Backwards)	4.00	3.22	3.87	0.511	–
Attentional matrices	42.2	41.9	40.0	0.845	24%
Short story	13.5	11.7	13.5	0.713	9%
Copy of figure delayed recall	0.65	0.61	0.48	0.184	21%
Copy of figure immediate recall	0.70	0.71	0.67	0.093	6%
Cancellation task (Total omissions)	1.40	1.74	3.39	0.221	26%
Cancellation task (Time)	138	136	144	0.527	51%
Nelson MCST (Categories)	4.3	4.4	5.0	0.317	12%
Nelson MCST (Perseverations)	4.8	4.7	3.3	0.350	21%
Hamilton rating depression scale	3.7	4.3	2.7	0.440	0

**p, probability for Friedman test; **UCO, percent of patients Under Cut Off in the sample as a whole.*

the MCID/MCD range (see means in **Figure 2**). Results survived Bonferroni correction ($p < 0.016$).

ARAT had a very similar progression for both groups and the two sequential protocols (**Figure 3**), reaching the MCID/MCD range only after the second intervention. Only time had a significant effect ($F = 3.54$, $p = 0.002$) but not priming stimulation ($F = 0.35$, $p = 0.565$) or interaction ($F = 0.13$, $p = 0.99$), the *post-hoc* analysis showed that there were higher values at the end of the second cycle of NIBS (second long follow-up = second short follow-up = second cycle of NIBS > baseline, after one cycle of NIBS, short and long follow-up and after pause).

Time had a significant effect on both N200 ($F = 41.9$, $p < 0.001$, $\eta^2 = 0.2$) and P300 ($F = 115.1$, $p < 0.001$, $\eta^2 = 0.4$) latencies. The electrode was not significant for both N200 ($F = 0.6$, $p = 0.830$) and P300 ($F = 0.4$, $p = 0.922$). The intervention was significant on both N200 ($F = 16.2$, $p < 0.001$, $\eta^2 = 0.1$) and P300 ($F = 8.6$, $p < 0.001$, $\eta^2 = 0.1$). A significant interaction term time by intervention was found for N200 ($F = 5.1$ $p = 0.007$, $\eta^2 = 0.1$) and P300 ($F = 34.3$, $p < 0.001$, $\eta^2 = 0.3$). Results survived Bonferroni correction ($p < 0.016$). Other interactions terms were all not significant for N200 and P300.

In the *post-hoc* analyses the N200 and P300 latencies in the second time point were significantly shorter, sham group had shorter latencies at baseline, and interaction depends by a greater lowering in the rTMS+tDCS (N200 = 22 ms, P300 = 32 ms) and tDCS+rTMS (N200 = 21 ms, P300 = 36 ms) groups compared to sham (N200 = 6 ms, P300 = 1 ms).

Time was only significant for the copy of figure with immediate recall ($F = 5.9$, $p = 0.006$, $\eta^2 = 0.2$), as was time

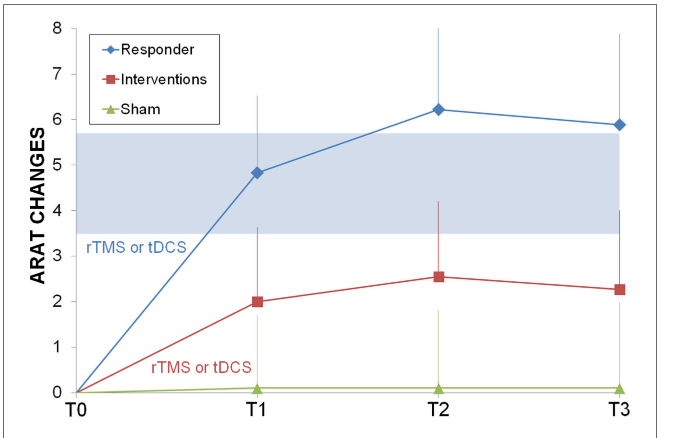


FIGURE 2 | Longitudinal psyiatric evaluation. ARAT changes from baseline were shown for sham control group (light green triangle), interventions group (rTMS or tDCS, red squares) and responder subgroup (ARAT T1> ARAT T0, blue diamonds). In light blue the range of Minimally Important Clinical Difference. Abbreviations as in **Figure 1**.

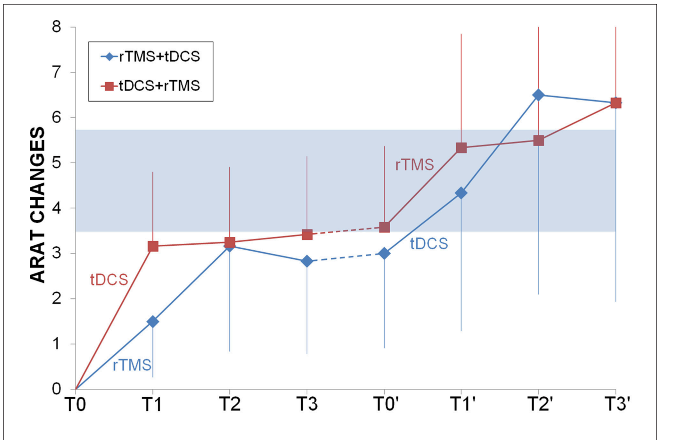


FIGURE 3 | Longitudinal comparison between rTMS and tDCS. ARAT changes from baseline were shown for rTMS+tDCS (blue diamonds) and tDCS+rTMS (red squares) groups. Dotted lines indicated washout. In light blue the range of Minimally Important Clinical Difference. Abbreviations as in **Figure 1**.

by intervention interaction ($F = 4.6$, $p = 0.004$, $\eta^2 = 0.3$), but not for intervention ($F = 0.6$, $p = 0.568$). In the *post-hoc* analyses rTMS+tDCS and tDCS+rTMS groups had a similar stable improvement that the sham group did not show.

For both ERP and NPS the sequence of priming was not significant.

Study 2—Comparison of tDCS and rTMS Clinical Efficacy

The change in ARAT score did not differ between tDCS or rTMS neither in the total sample nor in the responders subgroup. Also, the ARAT profiles were similar for rTMS and tDCS. Respectively, the scores were: gross movements 0.8 vs. 0.7, grasp 1.6 vs. 2.3, grip 0.4 vs. 0.8, pinch 0.9 vs. 0.7, showing the same qualitative improvements.

N200 and P300 had a very similar changes induced by rTMS and tDCS, as both interventions were able to shorten the ERP but only temporally, because after the washout the latencies return to the baseline values (**Figure 4**).

Time had a significant effect only for four tests: the copy of figure with immediate recall was significant for the sham-tDCS group ($\chi^2 = 8.0$, $p = 0.037$), for the dual-tDCS group ($\chi^2 = 15.9$, $p < 0.001$) and for the rTMS group ($\chi^2 = 8.6$, $p = 0.015$). Time was a significant factor for the other three tests only in the dual-tDCS group: copy of figure with delayed recall ($\chi^2 = 25.7$, $p < 0.001$), attentional matrices ($\chi^2 = 6.2$, $p = 0.043$), and perseverations in the Nelson's MCST test ($\chi^2 = 7.1$, $p = 0.027$). See **Table 3** for *post-hoc* tests and average differences. Only some results survived Bonferroni correction ($p < 0.016$).

Study 3—Cognitive Differences in Patients That Responded to Motor Rehabilitation

At baseline, after one or two cycles of treatment there were no differences in ERP or NPS between responders and no-responders.

DISCUSSION

In partial disagreement with previous results (Patel et al., 2002; Mehta et al., 2003; Saxena et al., 2007; Rabadi et al., 2008), the present study shows improvements in motor and cognitive performances even in patients with chronic stroke presenting some cognitive deficits (responders and no-responders did not differ for ERP or NPS at baseline) after NIBS treatment.

In the present study patients with cognitive impairment (MMSE < 25) have been excluded, in order to reduce confounding factors, but focal deficits were detected in some patients, mostly with left hemisphere lesions (**Tables 1, 2**). This finding could be explained by many factors. First, we evaluated many different cognitive domains and did not rely only on less sensitive screening tests as in the majority of previous studies (Carter et al., 1988; Barker-Collo et al., 2009; Winkens et al., 2009; Hoffmann et al., 2010; McPhail et al., 2014). Furthermore NIBS stimulations (rTMS or dual-tDCS), producing long lasting effect on cortical plasticity (Miniussi et al., 2008), could promote motor and cognitive improvement also in chronic patients, who traditionally are believed to be stable and not suitable for rehabilitation. The impairment in some cognitive domains should, thus, not be considered an exclusion criterion for rehabilitation in NIBS training programs.

The interventions were safe and tolerated (**Table 1**) and had a partial efficacy.

Motor improvement in hands' functionality, measured with ARAT, was observed after NIBS treatment in a large percentage of patients (44%), but not after sham (**Figure 2**). The effect was stable in time (baseline < intervention and follow-up) and it was similar for dual-tDCS and rTMS at every time point (**Figure 3**). Looking at the additive effects of two cycles of intervention we can observe that, regardless the techniques used first for priming, the conjoint effects were significant on the clinical outcome (ARAT difference > MCID/MCD 3.5–5.7).

ERP endogenous components (N200 and P300) reflect perceptual and cognitive processing and can play an important role in testing stroke patients (Hillyard and Kutas, 1983); for instance, Alonso-Prieto et al. (2002) demonstrated the high sensitivity of P300 in detecting alterations of sustained attention in stroke patients with right parietal lesion.

Stahlhut et al. (2014) reported ERP data of 563 stroke patients within 4 weeks, after 12 and 24 months from the ischemic event. In this paper, a lengthened P300 latency at baseline in 51% of the patients, similar for left or right lesions, was reported with a significant improvement after 24 months (about 20 ms), similar for left and right hemispheric infarction.

In previous reports, the authors measured P300 latencies at Pz or Cz (Trinka et al., 2000; Alonso-Prieto et al., 2002; Yamagata

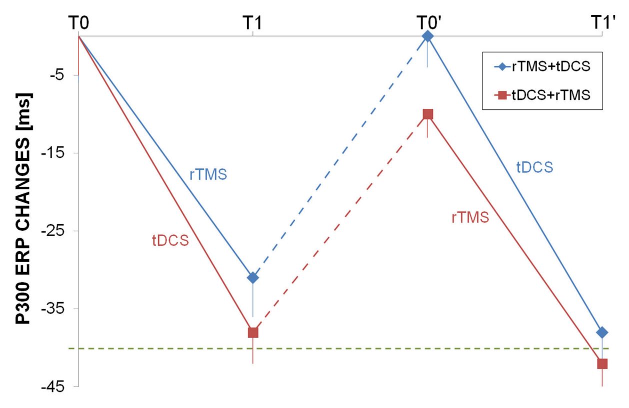


FIGURE 4 | Longitudinal auditory evoked potential evaluation. P300 changes from baseline were shown for rTMS+tDCS (blue diamonds) and tDCS+rTMS (red squares) groups. Dotted blue and red lines indicated washout. The dotted green line was at 40 ms improvement as reference. Abbreviations as in **Figure 1**.

TABLE 3 | Longitudinal effects of treatments onto the neuropsychological scores.

Time points	t0–t1		t1–t2		t0–t2	
SHAM-tDCS						
Copy of figure immediate recall	$p = 0.025$	0.5	$p = 0.990$	NS	$p = 0.157$	NS
rTMS						
Copy of figure immediate recall	$p = 0.008$	0.25	$p = 0.380$	NS	$p = 0.260$	NS
DUAL-tDCS						
Copy of figure delayed recall	$p = 0.001$	0.36	$p = 0.317$	NS	$p = 0.002$	0.35
Copy of figure immediate recall	$p = 0.005$	0.25	$p = 0.317$	NS	$p < 0.001$	0.4
Attentional matrices	$p = 0.050$	3.6	$p = 0.822$	NS	$p = 0.023$	3.1
Nelson MCST perseveration	$p = 0.048$	−11	$p = 0.122$	NS	$p = 0.778$	NS

t0–t1, differences between baseline and after treatment; t1–t2, differences between treatment and follow-up; t0–t2, differences between baseline and follow-up; NS, not significant; p, probability for Wilcoxon test.

et al., 2004; Stahlhut et al., 2014) while in our study we used a finer setup and ERP latencies has been computed at F3, F4, F7, F8, C3, C4, P3, P4, T3, T4. No significant difference has been observed in P300 latency values measured on right or left hemisphere's electrodes. The finding of P300 latency lengthening in the baseline EEG mirrored the focal impairment in attention domain that has been observed in many of our patients (**Table 2**). rTMS or dual-tDCS + MT, compared to sham-tDCS, had similar effects: treated patients showed a significant improvement in P300 latencies (of about 30 ms), but the improvement was transient and lost after the 6-months washout period.

The positive effect on P300 latency, after NIBS, is an additional unspecific improvement, linked to attentional networks functionality, achieved by transient modification of neuronal plasticity. Although not permanent, it could be used in the rehabilitation of chronic patients because it could produce a greater compliance and it should be possibly used to promote simultaneous neurocognitive training (e.g., visuospatial skills and MT). On the other hand, ERP were not useful to predict long term outcome and to identify responders or as a surrogate quantitative marker of the effect of NIBS.

The cognitive improvement was prevalently observed in dual-tDCS + MT for tests that are mainly influenced by the visuospatial domain (spatial attention, spatial memory, visuoconstructive skills). While some results were also found in TMS or in sham + MT they were not stable at follow-up as were instead in dual-tDCS + MT. This could be interpreted as an effect of neural plasticity that strengthened and stabilized the MT rehabilitation training. This result is not surprising as MT could enhance spatial coupling, as previously argued by Michielsen et al. Indeed, they hypothesized that the mirror illusion could increase the tendency of one limb to take on the spatial properties of the other (Michielsen et al., 2011). The effects anyway were moderate (3–8%), they did not impact dramatically on clinical outcome in a single run. We could not look at conjoint effects of the two interventions as only dual-tDCS impacted on cognition in the long run.

In our study stimulation has been performed on M1 of the unaffected hemisphere with inhibitory low frequency rTMS, or on M1 of both hemispheres with dual-TMS (excitatory anodal-tDCS on affected hemisphere and inhibitory cathodal-tDCS on unaffected hemisphere). Consequently, cortical stimulation targets have been chosen in order to improve plasticity of cortical and sub-cortical motor networks and not specifically of cognitive networks. Nevertheless, a transient cognitive improvement has been observed after each NIBS technique. These observations demonstrate that the actual knowledge of physiological mechanisms underlying NIBS techniques is still very limited. In fact, many different cortical targets have been stimulated with many different NIBS techniques (single-pulse TMS, low frequency rTMS, high frequency rTMS, anodal-tDCS, cathodal-tDCS, dual-tDCS) to improve cortical plasticity in cognitive rehabilitation protocols on attention domain, but results are contradictory (Seyal et al., 1995; Oliveri et al., 1999, 2000, 2001; Hilgetag et al., 2001; Brighina et al., 2003; Shindo et al., 2006; Ragert et al., 2008). Hence, we could hypothesize that brain stimulation effects on neuronal activity of a specific target areas are wide and not easily predictable. Moreover, even if physiological mechanisms of rTMS and tDCS are known to be different (Schlaug et al., 2008; Lefaucheur et al., 2014; Lüdemann-Podubecká et al., 2014), we did not detected any difference in motor or ERP improvement. Only one previous work (Simis et al., 2013) led a comparison between these two NIBS techniques in healthy subjects, observing that both techniques induced similar motor gains, but opposite results in cortical excitability, confirming the lack of complete understanding of the physiological processes induced by NIBS. In our study the observed effects of NIBS may be related to the direct change of activity in brain areas immediately beneath the stimulation site or, more probably, may involve more extensively connected neural networks. This is supported by previous works that demonstrated that rTMS and anodal-tDCS can induce modification of cortical activity both locally and in distant sites (Lang et al., 2005; Sack et al., 2007; Ruff et al., 2008).

Even if the precise mechanisms underlying NIBS techniques remain unclear, the modification of cortical excitability may promote adaptive neural reorganization or interrupt maladaptive functional mechanisms. These mechanisms, such as inter-hemispheric inhibition, can limit recovery by inhibition of perilesional brain areas (Murase et al., 2004; Ward and Cohen, 2004), restoring a correct balance between damaged and undamaged hemisphere and promoting behavioral recovery (Pascual-Leone, 2006; Miniussi et al., 2008). Furthermore, even if this facilitatory effect is transient, NIBS application in concomitance with rehabilitative training that supports learning processes may perpetuate the behavioral effects further, beyond the end of stimulation (Rossi and Rossini, 2004; Pascual-Leone, 2006).

The observation that rTMS and dual-tDCS have similar effects on brain plasticity could have important practical implications in neuro-rehabilitation. First, tDCS has some advantages, it is a simple and portable device, it is a non-expensive procedure, painless, and without severe collateral effects. Moreover, tDCS devices are wearable and can be used to stimulate patients online during more complex motor or cognitive training also in parallel, as in our experiment. Finally, tDCS allows an easy and reliable sham condition, which allows double blind clinical trials. However, its major limitation is that it is not as focal as TMS, so it does not allow an accurate mapping of cortical areas. Nevertheless, our data showed that it is possible to obtain satisfactory results integrating tDCS with the MT directing the modulatory effects onto the upper limb and, at the same time, improving cognitive performances.

This study suggests that the slow improvement in motor learning due to the memory stabilization (Wessel et al., 2015) could be an important factor in NIBS rehabilitation, in addition to other parameters. Also the number of cycles and the interval between them should be considered and investigated in future. The great variability in the response to NIBS, shown even by healthy subjects (Wiethoff et al., 2014; Strube et al., 2015), compels investigators to find reliable predictors of induced plasticity changes (e.g., neuroimaging characteristics, clinical features) in patients undergoing rehabilitation.

STUDY LIMITATIONS

Some limits should be taken in considerations:

Our sample was relatively small and heterogeneous, so it should be replied in a larger randomized clinical trial. The best candidate is a MT intervention with real and sham dual-tDCS.
The study protocol did not include imaging (CT or MRI), so it was impossible to provide a precise functional map of the damaged cortical and subcortical areas.
There were some differences in N200 and P300 at baseline in the different groups.
rTMS was underpowered compared to tDCS as in the second arm two interventions (tDCS + MT) were administered, but it was not feasible to use MT online with TMS;
The poor knowledge of physiologic mechanisms could limit the interpretations of our results.

CONCLUSIONS

The present study allows some practical considerations, useful for neuro-rehabilitation:

First the impairment in some cognitive domains cannot be considered an exclusion criterion for rehabilitation with NIBS.
Second, NIBS generally improved ERP, but transitorily.
Third, attentive processes depend on different cortical areas and may improve with brain stimulation, also on M1, perhaps because of restoring the hemispheric balance or by distant connections effects.
Finally, NIBS effects were comparable, but there are some advantages of using tDCS vs. rTMS in stroke rehabilitation. More than one NIBS cycle (2–4 weeks) should be used in rehabilitation to obtain clinical relevant results after a washout period only in responder patients.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

Alonso-Prieto, E., Alvarez-González, M. A., Fernández-Concepción, O., Jiménez-Conde, A., and Machado, C. (2002). Usefulness of P300 as a tool for diagnosing alterations in sustained attention in ischemic cerebrovascular disease. *Rev. Neurol.* 34, 1105–1109.

Barker-Collo, S. L., Feigin, V. L., Lawes, C. M. M., Parag, V., Senior, H., and Rodgers, A. (2009). Reducing attention deficits after stroke using attention process training: A randomized controlled trial. *Stroke* 40, 3293–3298. doi: 10.1161/STROKEAHA.109.558239

Bikson, M., Name, A., and Rahman, A. (2013). Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Front. Hum. Neurosci.* 7:688. doi: 10.3389/fnhum.2013.00688

Bliss, T. V. P., and Cooke, S. F. (2011). Long-term potentiation and long-term depression: a clinical perspective. *Clinics (Sao Paulo)* 66(Suppl. 1), 3–17. doi: 10.1590/S1807-59322011001300002

Bolognini, N., Pascual-Leone, A., and Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *J. Neuroeng. Rehabil.* 6:8. doi: 10.1186/1743-0003-6-8

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., La Bua, V., Daniele, O., et al. (2003). 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neurosci. Lett.* 336, 131–133. doi: 10.1016/S0304-3940(02)01283-1

Carter, L. T., Oliveira, D. O., Duponte, J., and Lynch, S. V. (1988). The relationship of cognitive skills performance to activities of daily living in stroke patients. *Am. J. Occup. Ther. Off.* 42, 449–455. doi: 10.5014/ajot.42.7.449

Connell, L. A., and Tyson, S. F. (2012). Clinical reality of measuring upper-limb ability in neurologic conditions: a systematic review. *Arch. Phys. Med. Rehabil.* 93, 221–228. doi: 10.1016/j.apmr.2011.09.015

Dinteren, R., Arns, M., Jongsma, M. L. A., and Kessels, R. P. C. (2014). P300 development across the lifespan: a systematic review and meta-analysis. *PLoS ONE* 9:e87347. doi: 10.1371/journal.pone.0087347

Dohle, C., Püllen, J., Nakaten, A., Küst, J., Rietz, C., and Karbe, H. (2009). Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. *Neurorehabil. Neural Repair* 23, 209–217. doi: 10.1177/1545968308324786

Ebrahim, S., Nouri, F., and Barer, D. (1985). Cognitive impairment after stroke. *Age Ageing* 14, 345–348. doi: 10.1093/ageing/14.6.345

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. *Neuron* 66, 198–204. doi: 10.1016/j.neuron.2010.03.035

Goodin, D., Desmedt, J., Maurer, K., and Nuwer, M. R. (1994). IFCN recommended standards for long-latency auditory event-related potentials. Report of an IFCN committee. *Electroencephalogr. Clin. Neurophysiol.* 91, 18–20. doi: 10.1016/0013-4694(94)90014-0

Hamilton, M. (1980). Rating depressive patients. *J. Clin. Psychiatry* 41, 21–24.

Hilgetag, C. C., Théoret, H., and Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced "virtual lesions" of human parietal cortex. *Nat. Neurosci.* 4, 953–957. doi: 10.1038/nn0901-953

Hillyard, S. A., and Kutas, M. (1983). Electrophysiology of cognitive processing. *Annu. Rev. Psychol.* 34, 33–61. doi: 10.1146/annurev.ps.34.020183.000341

Hoffmann, T., Bennett, S., Koh, C.-L., and McKenna, K. (2010). A systematic review of cognitive interventions to improve functional ability in people who have cognitive impairment following stroke. *Top. Stroke Rehabil.* 17, 99–107. doi: 10.1310/tsr1702-99

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., et al. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 128, 490–499. doi: 10.1093/brain/awh369

Hummel, F. C., and Cohen, L. G. (2006). Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol.* 5, 708–712. doi: 10.1016/s1474-4422(06)70525-7

Lang, N., Siebner, H. R., Ward, N. S, Lee, L., Nitsche, M. A., Paulus, W., et al. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur. J. Neurosci.* 22, 495–504. doi: 10.1111/j.1460-9568.2005.04233.x

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., et al. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin. Neurophysiol.* 125, 2150–2126. doi: 10.1016/j.clinph.2014.05.021

Liew, S.-L., Santarnecchi, E., Buch, E. R., and Cohen, L. G. (2014). Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. *Front. Hum. Neurosci.* 8:378. doi: 10.3389/fnhum.2014.00378

Lin, J.-H., Hsu, M.-J., Sheu, C.-F., Wu, T.-S., Lin, R.-T., Chen, C.-H., et al. (2009). Psychometric comparisons of 4 measures for assessing upper-extremity function in people with stroke. *Phys. Ther.* 89, 840–850. doi: 10.2522/ptj.20080285

Lüdemann-Podubecká, J., Bösl, K., Rothhardt, S., Verheyden, G., and Nowak, D. A. (2014). Transcranial direct current stimulation for motor recovery of upper limb function after stroke. *Neurosci. Biobehav. Rev.* 47, 245–259. doi: 10.1016/j.neubiorev.2014.07.022

McPhail, S. M., Varghese, P. N., and Kuys, S. S. (2014). Patients undergoing subacute physical rehabilitation following an acute hospital admission demonstrated improvement in cognitive functional task independence. *Scientific World Journal* 2014:810418 . doi: 10.1155/2014/810418

Mehta, K. M., Yaffe, K., Langa, K. M., Sands, L., Whooley, M. A., and Covinsky, K. E. (2003). Additive effects of cognitive function and depressive symptoms on mortality in elderly community-living adults. *J. Gerontol. A. Biol. Sci. Med. Sci.* 58, M461–M467. doi: 10.1093/gerona/58.5.m461

Michielsen, M. E., Smits, M., Ribbers, G. M., Stam, H. J., van der Geest, J. N., Bussmann, J. B. J., et al. (2011). The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke. *J. Neurol. Neurosurg. Psychiatry* 82, 393–398. doi: 10.1136/jnnp.2009.194134

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., et al. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimul.* 1, 326–336. doi: 10.1016/j.brs.2008.07.002

Murase, N., Duque, J., Mazzocchio, R., and Cohen, L. G. (2004). Influence of interhemispheric interactions on motor function in chronic stroke. *Ann. Neurol.* 55, 400–409. doi: 10.1002/ana.10848

Oliveri, M., Bisiach, E., Brighina, F., Piazza, A., La Bua, V., Buffa, D., et al. (2001). rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology* 57, 1338–1340. doi: 10.1212/WNL.57.7.1338

Oliveri, M., Rossini, P. M., Filippi, M. M., Traversa, R., Cicinelli, P., Palmieri, M. G., et al. (2000). Time-dependent activation of parieto-frontal networks for directing attention to tactile space. A study with paired transcranial magnetic stimulation pulses in right-brain-damaged patients with extinction. *Brain* 123(Pt 9), 1939–1947. doi: 10.1093/brain/123.9.1939

Oliveri, M., Rossini, P. M., Pasqualetti, P., Traversa, R., Cicinelli, P., Palmieri, M. G., et al. (1999). Interhemispheric asymmetries in the perception of unimanual and bimanual cutaneous stimuli. A study using transcranial magnetic stimulation. *Brain* 122, 1721–1729. doi: 10.1093/brain/122.9.1721

Pandian, S., and Arya, K. N. (2014). Stroke-related motor outcome measures: do they quantify the neurophysiological aspects of upper extremity recovery? *J. Bodyw. Mov. Ther.* 18, 412–423. doi: 10.1016/j.jbmt.2013.11.006

Pascual-Leone, A. (2006). Disrupting the brain to guide plasticity and improve behavior. *Prog. Brain Res.* 157, 315–329. doi: 10.1016/S0079-6123(06)57019-0

Patel, M. D., Coshall, C., Rudd, A. G., and Wolfe, C. D. A. (2002). Cognitive impairment after stroke: clinical determinants and its associations with long-term stroke outcomes. *J. Am. Geriatr. Soc.* 50, 700–706. doi: 10.1046/j.1532-5415.2002.50165.x

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., et al. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database Syst. Rev.* 11:CD010820. doi: 10.1002/14651858.CD010820.pub2

Rabadi, M. H., Rabadi, F. M., Edelstein, L., and Peterson, M. (2008). Cognitively impaired stroke patients do benefit from admission to an acute rehabilitation unit. *Arch. Phys. Med. Rehabil.* 89, 441–448. doi: 10.1016/j.apmr.2007.11.014

Ragert, P., Vandermeeren, Y., Camus, M., and Cohen, L. G. (2008). Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clin. Neurophysiol.* 119, 805–811. doi: 10.1016/j.clinph.2007.12.001

Ramachandran, V. S., Rogers-Ramachandran, D., and Cobb, S. (1995). Touching the phantom limb. *Nature* 377, 489–490. doi: 10.1038/377489a0

Rossi, S., and Rossini, P. M. (2004). TMS in cognitive plasticity and the potential for rehabilitation. *Trends Cogn. Sci.* 8, 273–279. doi: 10.1016/j.tics.2004.04.012

Ruff, C. C., Bestmann, S., Blankenburg, F., Bjoertomt, O., Josephs, O., Weiskopf, N., et al. (2008). Distinct causal influences of parietal versus frontal areas on human visual cortex: evidence from concurrent TMS-fMRI. *Cereb. Cortex* 18, 817–827. doi: 10.1093/cercor/bhm128

Sack, A. T., Kohler, A., Bestmann, S., Linden, D. E. J., Dechent, P., Goebel, R., et al. (2007). Imaging the brain activity changes underlying impaired visuospatial judgments: simultaneous fMRI, TMS, and behavioral studies. *Cereb. Cortex* 17, 2841–2852. doi: 10.1093/cercor/bhm013

Sandrini, M., and Cohen, L. G. (2013). Noninvasive brain stimulation in neurorehabilitation. *Handb. Clin. Neurol.* 116, 499–524. doi: 10.1016/B978-0-444-53497-2.00040-1

Saxena, S. K., Ng, T. P., Koh, G., Yong, D., and Fong, N. P. (2007). Is improvement in impaired cognition and depressive symptoms in post-stroke patients associated with recovery in activities of daily living? *Acta Neurol. Scand.* 115, 339–346. doi: 10.1111/j.1600-0404.2006.00751.x

Schlaug, G., Renga, V., and Nair, D. (2008). Transcranial direct current stimulation in stroke recovery. *Arch. Neurol.* 65, 1571–1576. doi: 10.1001/archneur.65.12.1571

Seyal, M., Ro, T., and Rafal, R. (1995). Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe. *Ann. Neurol.* 38, 264–267. doi: 10.1002/ana.410380221

Shindo, K., Sugiyama, K., Huabao, L., Nishijima, K., Kondo, T., and Izumi, S.-I. (2006). Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. *J. Rehabil. Med.* 38, 65–67. doi: 10.1080/16501970500441807

Simis, M., Adeyemo, B. O., Medeiros, L. F., Miraval, F., Gagliardi, R. J., and Fregni, F. (2013). Motor cortex-induced plasticity by noninvasive brain stimulation: a comparison between transcranial direct current stimulation and transcranial magnetic stimulation. *Neuroreport* 24, 973–975. doi: 10.1097/WNR.0000000000000021

Spinnler, H., and Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Ital. J. Neurol. Sci.* 6(Suppl 8), 1–120.

Stahlhut, L., Grotemeyer, K.-H., Husstedt, I.-W., and Evers, S. (2014). The impact of stroke on cognitive processing - a prospective event-related potential study. *J. Neurol. Sci.* 339, 157–163. doi: 10.1016/j.jns.2014.02.006

Strube, W., Bunse, T., Malchow, B., and Hasan, A. (2015). Efficacy and interindividual variability in motor-cortex plasticity following anodal tDCS and paired-associative stimulation. *Neural Plast.* 2015:530423. doi: 10.1155/2015/530423

Tatemichi, T. K., Desmond, D. W., Stern, Y., Paik, M., Sano, M., and Bagiella, E. (1994). Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J. Neurol. Neurosurg. Psychiatry* 57, 202–207. doi: 10.1136/jnnp.57.2.202

Thickbroom, G. W. (2007). Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. *Exp. Brain Res.* 180, 583–593. doi: 10.1007/s00221-007-0991-3

Trinka, E., Unterrainer, J., Staffen, W., Löscher, N. W., and Ladurner, G. (2000). Delayed visual P3 in unilateral thalamic stroke. *Eur. J. Neurol.* 7, 517–522. doi: 10.1046/j.1468-1331.2000.t01-1-00117.x

Van der Lee, J. H., De Groot, V., Beckerman, H., Wagenaar, R. C., Lankhorst, G. J., and Bouter, L. M. (2001). The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. *Arch. Phys. Med. Rehabil.* 82, 14–19. doi: 10.1053/apmr.2001.18668

Ward, N. S., and Cohen, L. G. (2004). Mechanisms underlying recovery of motor function after stroke. *Arch. Neurol.* 61, 1844–1848. doi: 10.1001/archneur.61.12.1844

Wessel, M. J., Zimerman, M., and Hummel, F. C. (2015). Non-invasive brain stimulation: an interventional tool for enhancing behavioral training after stroke. *Front. Hum. Neurosci.* 9:265. doi: 10.3389/fnhum.2015.00265

Wiethoff, S., Hamada, M., and Rothwell, J. C. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimul.* 7, 468–475. doi: 10.1016/j.brs.2014.02.003

Winkens, I., Van Heugten, C. M., Wade, D. T., Habets, E. J., and Fasotti, L. (2009). Efficacy of time pressure management in stroke patients with slowed information processing: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* 90, 1672–1679. doi: 10.1016/j.apmr.2009.04.016

Yamagata, S., Yamaguchi, S., and Kobayashi, S. (2004). Impaired novelty processing in apathy after subcortical stroke. *Stroke* 35, 1935–1940. doi: 10.1161/01.STR.0000135017.51144.c9

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 31 March 2016
doi: 10.3389/fnbeh.2016.00057

Concomitant Use of Transcranial Direct Current Stimulation and Computer-Assisted Training for the Rehabilitation of Attention in Traumatic Brain Injured Patients: Behavioral and Neuroimaging Results

Katiuscia Sacco[1,2], Valentina Galetto[1,3], Danilo Dimitri[1,3], Elisabetta Geda[1], Francesca Perotti[1], Marina Zettin[1,3] and Giuliano C. Geminiani[1,2]*

[1] Imaging and Cerebral Plasticity Research Group, Department of Psychology, University of Turin, Turin, Italy, [2] Neuroscience Institute of Turin, University of Turin, Turin, Italy, [3] Centro Puzzle, Turin, Italy

Divided attention (DA), the ability to distribute cognitive resources among two or more simultaneous tasks, may be severely compromised after traumatic brain injury (TBI), resulting in problems with numerous activities involved with daily living. So far, no research has investigated whether the use of non-invasive brain stimulation associated with neuropsychological rehabilitation might contribute to the recovery of such cognitive function. The main purpose of this study was to assess the effectiveness of 10 transcranial direct current stimulation (tDCS) sessions combined with computer-assisted training; it also intended to explore the neural modifications induced by the treatment. Thirty-two patients with severe TBI participated in the study: 16 were part of the experimental group, and 16 part of the control group. The treatment included 20’ of tDCS, administered twice a day for 5 days. The electrodes were placed on the dorso-lateral prefrontal cortex. Their location varied across patients and it depended on each participant’s specific area of damage. The control group received sham tDCS. After each tDCS session, the patient received computer-assisted cognitive training on DA for 40’. The results showed that the experimental group significantly improved in DA performance between pre- and post-treatment, showing faster reaction times (RTs), and fewer omissions. No improvement was detected between the baseline assessment (i.e., 1 month before treatment) and the pre-training assessment, or within the control group. Functional magnetic resonance imaging (fMRI) data, obtained on the experimental group during a DA task, showed post-treatment lower cerebral activations in the right superior temporal gyrus (BA 42), right and left middle frontal gyrus (BA 6), right postcentral gyrus (BA 3) and left inferior frontal gyrus (BA 9). We interpreted such neural changes as normalization of previously abnormal hyperactivations.

Keywords: transcranial direct current stimulation (tDCS), cognitive rehabilitation, attention, traumatic brain injury (TBI), functional magnetic resonance imaging (fMRI), cerebral plasticity

OPEN ACCESS

Edited by:
Nuno Sousa,
University of Minho, Portugal

Reviewed by:
Jason Moser,
Michigan State University, USA
Camila Cosmo,
Harvard Medical School, USA

***Correspondence:**
Valentina Galetto
valentinagaletto@virgilio.it

Received: *09 May 2015*
Accepted: *09 March 2016*
Published: *31 March 2016*

Citation:
Sacco K, Galetto V, Dimitri D, Geda E, Perotti F, Zettin M and Geminiani GC (2016) Concomitant Use of Transcranial Direct Current Stimulation and Computer-Assisted Training for the Rehabilitation of Attention in Traumatic Brain Injured Patients: Behavioral and Neuroimaging Results. Front. Behav. Neurosci. 10:57. doi: 10.3389/fnbeh.2016.00057

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of disability and social withdrawal in young individuals (Andelic et al., 2009). These patients typically require long-lasting and costly rehabilitation; the outcome, depending on many factors, may vary among cases. Rehabilitation research should, on the one hand, design and test the effectiveness of innovative rehabilitation strategies and on the other, identify how patients can benefit from different rehabilitation programs in order to maximize the individual chances of improvement. This is particularly important in the case of TBI patients, as their cerebral lesions and the neurobehavioral consequences vary greatly from one person to another.

Among the cognitive changes that may occur following TBI, the most prominent are divided attention (DA) and memory disorders (Asloun et al., 2008; Cyr et al., 2009). Indeed, patients, their caregivers and rehabilitation professionals frequently report their difficulty in doing two things simultaneously, and this difficulty may negatively impact on their return to work (van Zomeren and van den Burg, 1985; Ponsford and Clements, 1991; Couillet et al., 2010). Research on DA in patients with TBI has shown that they do not have any difficulty when the DA tasks can be carried out relatively automatically. On the contrary, they are impaired when the exercise becomes more complex or it needs to be performed under high time-pressure, requiring considerable working memory load or executive control (Park et al., 1999; Leclercq and Azouvi, 2002). For example, in the study conducted by Park et al. (1999) severe TBI patients and control subjects were asked to perform two tasks involving working memory. The exercises had to be executed first separately and then concurrently. The results showed that the TBI group had significantly more difficulties when performing the two tasks concurrently, although their performance does not statistically differ from that of healthy participants when the same tasks were done separately. In other studies involving patients with severe TBI, deficits in DA have only been found in the more demanding conditions (Brouwer et al., 2001, 2002). Most importantly, dual-task measures under the most difficult conditions seem to be strictly correlated with performance in daily-living activities, thus suggesting the key role of DA in everyday life (Withaar et al., 2000). Similar results were reported by Azouvi et al. (2004), who assessed dual-task performance in TBI patients, under three different experimental conditions, in which the participants were asked to pay equal attention to both tasks or to focus mostly on one of them. TBI patients only showed a disproportionate increase in reaction times (RTs) under the dual-task condition. All these results considered, DA should be one of the main targets in the rehabilitation of TBI patients, given its key role in many tasks of everyday life (Toyokura et al., 2012; Masson et al., 2013). However, few rehabilitation programs have been developed to improve this function in patients with TBI [(Couillet et al., 2010) specifically addressed DA; (Serino et al., 2007; Montani et al., 2014) included it in their training programs]. More generally, to date there is limited evidence of the effectiveness of cognitive rehabilitation programs aimed at improving attention (Cernich et al., 2010; Cicerone et al., 2011). Innovative rehabilitation strategies in this field are thus needed.

In this article, we present a training program for the rehabilitation of DA. We used a computer-based procedure: it has been demonstrated that the use of computer-assisted training leads to greater motivation, better training performance and better performance at post-training than using regular training (De Luca et al., 2014). A further innovative aspect of our trial was the use of neurostimulation procedures, which preceded every treatment session, in order to prepare the brain for the following exercises. Neurostimulation strategies using various forms of electrical stimulation have recently been applied to intervene on functional deficits in animal models and clinical trials. The main outcomes of these sets of research suggest a key role of neurostimulation in enhancing both motor and cognitive deficits after brain injury (Miniussi et al., 2008; Shin et al., 2015). Indeed, modifying cortical excitability may lead to a more functional neural reorganization (Villamar et al., 2012). Such techniques, aimed at boosting neuroplastic changes in the brain, are expected to enhance the effects of behavioral interventions in neurological diseases (Schulz et al., 2013; Clark and Parasuraman, 2014): cortical electrical stimulation combined with appropriate cognitive training may facilitate cerebral reorganization and consolidation of learning in the specifically trained neural networks. Among non-invasive brain stimulation techniques, transcranial direct current stimulation (tDCS) has recently gained consideration as it has shown promise in the enhancement of motor and cognitive functions (Flöel, 2014). It involves passing a direct electrical current through the cerebral cortex via electrodes placed upon the scalp. Although the passage of the electrical signal in the overlying tissues entails a partial current dispersion, the stimulus that reaches the brain is intense enough to change the resting membrane potential, thus modifying the level of spontaneous neuronal excitability. tDCS serves as a neuromodulatory intervention: our rehabilitation protocol, involving the concomitant use of tDCS and computer-assisted exercises in DA, is aimed at modulating neural plasticity to improve performance. We applied tDCS over the dorsolateral prefrontal cortex (DLPFC), given its essential role in bimodal DA. Indeed, many studies (Johnson and Zatorre, 2005, 2006; Wagner et al., 2006; Johnson et al., 2007) have demonstrated that dividing attention between simultaneous auditory and visual events leads to increased activity in the DLPFC. This area seems to be causally involved in DA: in a research by Johnson et al. (2007), it was demonstrated that inhibiting the activity of the left posterior DLPFC through slow rTMS induced a significant decrease of DA in most of the participants.

In order to evaluate the effectiveness of this rehabilitation program, we collected pre- and post-treatment behavioral assessment measures; we also used functional magnetic resonance imaging (fMRI) to monitor possible changes following the therapeutic intervention, which may unravel mechanisms of treatment-related neuroplasticity. We expect that the concomitant use of tDCS and a computerized training is more effective in improving the DA ability than the use of a computerized training alone. Also, we predict that such improvements are accompanied by cerebral modifications within networks involved in dual task processing: fronto-parietal regions have been identified to be specifically involved in processing more information at a time (Herath et al., 2001; Collette et al., 2005; Nebel et al., 2005), with the inferior and middle frontal gyri holding a crucial role (for a review, see Klingberg, 2000).

MATERIALS AND METHODS

Participants

Thirty-two adult patients with TBI completed the rehabilitation program: 16 patients (4 females and 12 males) participated as part of the experimental group, and 16 patients (2 female and 14 males) participated as part of the control group. Participants were randomly assigned to the experimental group or to the control one. The experimental group ranged in age from 18 to 65 years (M = 37.7; SD = 10.4); their level of education ranged from 8 to 18 years of schooling (M = 11.5; SD = 3.48). The control group ranged in age from 18 to 66 (M = 35,2; SD = 12,9), and their education level was comprised between 5 and 17 (M = 10,5; SD = 4,09). The two groups did not statistically differ with respect to age ($t = -0.488$; $p = 0.629$) and educational level ($t = -0.816$; $p = 0.421$). Participants were recruited at the Centro Puzzle, a local rehabilitation center for patients with severe brain injury. The time after onset ranged from 3.16 to 17.5 years (M = 8.73, SD = 4.45). All of the patients were victims of severe TBI: the Glasgow Coma Scale in the acute phase had been equal to or less than 8. The majority of the patients had sustained their injury in a road traffic accident. At the time of the study, all the patients were living at home, and none of them lived independently without their partners or parents.

Inclusion criteria for the study were the following: patients had to (1) be at least 18 years old; (2) be at least in their 12th month after the brain injury, in order to be sure that their cognitive profile was stable; (3) be Italian native speakers; (4) be in possession of adequate cognitive skills and comprehension abilities, certified by the achievement of a cut-off score of 24/30 on the Mini Mental State Examination (MMSE; Folstein et al., 1975) and of 29/36 on the Token Test (De Renzi and Vignolo, 1962). Exclusion criteria were the following: (1) prior history of TBI or other neurological disease; (2) neuropsychiatric illness; (3) pre-morbid alcohol or drug addiction, evaluated on the basis of the anamnestic data; (4) metal objects in the body such as aneurysm and hemostatic clips, implanted electrodes and electrical devices such as pacemakers, orthopedic material and devices. All of the participants gave their written informed consent to participate in the research. Approval for the study had previously been obtained from the local ethics committee (Centro Puzzle, protocol no. 1/2015).

Experimental Design and Behavioral Measures

The study was conducted over a period of 9 weeks, comprising a 5-day period of treatment and four assessment sessions (see **Figure 1**).

T0_Baseline

One month before the beginning of the treatment, the attentional abilities of the recruited patients were assessed using the DA subtest of the Test for the Examination of Attention (TEA; Zimmermann and Fimm, 2002). It consisted of a visual and an auditory computer-based task, which had to be performed simultaneously. Participants were asked to look at patterns of stimuli (letter X) moving on a computer screen, and to press a key only when they were in a specific arrangement. At the same time, they listened to high and low pitched sounds, and had to press a button only when the same pitch was repeated twice in succession. Moreover, the Repeatable Battery for the Assessment of the Neuropsychological Status (RBANS; Randolph et al., 1998) comprises tests of visual-spatial abilities, semantic fluency, selected attention, working memory and long-term memory, and it was administered to provide an evaluation of patients' abilities in different cognitive domains. Finally, the Beck's Depression Inventory (BDI; Beck et al., 1961) and

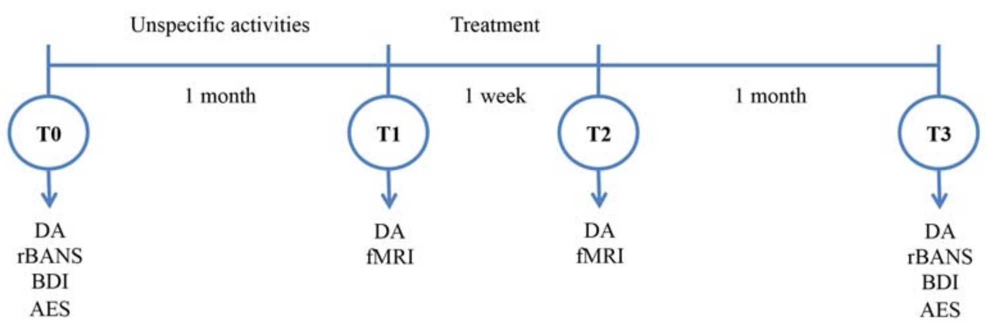


FIGURE 1 | Experimental design. DA, Divided Attention; RBANS, Repeatable Battery for the Assessment of the Neuropsychological Status; BDI, Beck's Depression Inventory; AES, Apathy Evaluation Scale.

the Apathy Evaluation Scale (AES; Marin et al., 1991) were administered to investigate whether a possible improvement of attention abilities might result in an enhancement of the affective state and therefore, in a significant reduction of depression and apathy. After the assessment, patients attended two sessions a week, for 1 month, during which they engaged in activities which were not specifically focused on improving attention. These included socializing activities, such as group recreation and games, as well as intellectual and creative activities, like reading newspapers, cooking and painting. The aim of this procedure was to detect any improvements in patients' attentional abilities due to spontaneous recovery, or as a consequence of unspecific activities, or of simply taking part in a research program.

T1_Pre-Treatment

A few days before the beginning of the treatment, the patients' attentional abilities were re-assessed with the DA subtest of the TEA, in order to verify the absence of any improvement due to attending sessions of unspecific activities between T0 and T1. Patients belonging to the experimental group also underwent the pre-treatment fMRI examination while performing a DA task.

T2_Post-Treatment

Immediately after the end of the treatment, the DA subtest of the TEA was administered to the participants for the third time, in order to prove the efficacy of the treatment on their attentional performance. Patients belonging to the experimental group also underwent the post-treatment fMRI examination to evaluate the changes that had occurred.

T3_FollowUp

One month after the end of the rehabilitation program the patients' attentional and cognitive abilities were reassessed using the RBANS and the DA subtest of TEA, to evaluate the stability of their improvements in time. The BDI and AES were administered for the second time.

In order to rule out learning effects, in the DA test stimuli appeared randomly on the computer screen, and parallel versions of the RBANS were used at the different time points.

fMRI Task

In addition to the behavioral assessment, patients underwent an fMRI scan before and after the treatment, in order to evaluate any changes in neuronal activity attributable to the treatment. Data acquisition was performed at the Koelliker Hospital in Turin, on a 1.5-T Philips Intera with a Sense high field high resolution head coil optimized for functional imaging. Patients with anxiety disorders such as claustrophobia, panic attacks or any disorder which could be severely exacerbated by confined spaces were excluded. A total of 11 patients completed the exam. In case of an emergency, the patients could press a button in order to ask for help and if necessary, interrupt the procedure at any time.

Functional areas of activations were assessed with a crossmodal DA task (Jackson et al., 2011). The task involved visual and auditory stimuli presented in an epoch-based design. During the task, visual stimuli (the letters "M" and "W" in white font on black background) were projected onto a screen using an LCD projector, and the images were viewed via a mirror positioned approximately 11 cm above the subject's eyes on the head coil. Auditory stimuli were played through headphones (two sinusoidal pure tones, 1500 Hz and 500 Hz, 16 bit stereo at 44.1 kHz). Each stimulus was presented for 300 ms with a variable interstimulus interval of between 400 ms and 1000 ms. The task consisted of four conditions (baseline, visual selective attention (VA), auditory selective attention, and DA) each lasting for five acquisition volumes (16 s) that were repeated eight times in a random sequence. For each subject, a stimulus for each of the visual and auditory modalities was randomly selected as the target stimulus (or stimuli) for each condition. Targets were presented with a 20% probability, and the subjects' task was to press a corresponding response button on an MR compatible keypad that they held in their dominant hand. Subjects were instructed to fixate on a cross hair on a screen in front of them during all different epochs. At the start of each block, instructions were displayed on the screen for 4 s: for baseline epochs subjects passively observed the sounds and letters; for VA selective epochs, subjects pressed the right response button every time their visual target (either an M or a W) appeared on the screen and ignored the tones; for auditory selective attention (AA) epochs, subjects pressed the left response button when they heard their target tone (either a 1500 Hz or 500 Hz tone) and ignored the letters; and for DA epochs, subjects pressed the right button when the target letter appeared on the screen, and the left button when the target tone was heard. A rest period, during which no task was presented, was given halfway through the task for eight volumes (25.6 s). A practice session was completed in a mock scanner before each session to minimize practice effects, and to familiarize subjects with the scanning environment. Finally, a set of anatomical MRI images were acquired (10 min).

Treatment

The treatment consisted of 10 sessions. each session included 20 min of tDCS stimulation followed by 30 min of DA training. The control group received 25 s of tDCS stimulation, then the device turned off automatically (sham conditions). The treatment was provided in two sessions per day and lasted 5 days (for recommended number of sessions and tDCS treatment duration see Scelzo et al., 2011). Each session lasted approximately 1 h. Both electrode montage and rehabilitation activities were performed by a trained psychologist, who was assisted by a neurologist, to intervene if and when necessary. The experiment was conducted in a quiet room, in the rehabilitation center where the participants were recruited. The treatment focused on DA: all the activities were designed to increase participants' ability to perform two tasks simultaneously. Specifically, they were asked to pay attention to auditory stimuli while performing VA tasks.

The tDCS stimulation was performed using a HDCstim device (Newronika srl, Milan, Italy). The electrodes (5 × 7 cm) were placed over the DLPFC, given its essential role in bimodal DA (Wagner et al., 2006; Johnson et al., 2007). However, the tDCS site differed between patients depending on the area of lesion, determined on the basis of the anatomical MRI scan. For those who had been excluded from the neuroimaging exam the electrode placement was established through the consultation of their clinical history and their previous scans. Overall, a dual channel stimulation (two anodes, one on the right DLPFC and the other on the left DLPFC, earth on the arm) was used with six patients having an equal hemispheric lesion distribution, while a mono channel stimulation was used with ten patients having unilateral lesions (anode on the lesioned hemisphere and cathode on the other hemisphere). In both cases the current intensity was 2 mA and its density 0.057 mA/cm^2. Both these indexes were kept below the safety limits (Poreisz et al., 2007). Participants' tolerance of the stimulation was constantly monitored. Furthermore, at the end of the procedure, each subject was invited to fill out a brief questionnaire on the adverse effects of the stimulation.

Statistical Analysis

Paired t-test analyses were conducted in order to evaluate improvements between baseline and pre-training (where we expected no difference) and between pre-training and post-training (where we expected significant differences in performance on the DA task within the experimental but not within the control group). Paired t-tests on the other tasks' measures were computed with the aim of exploring whether changes in other cognitive domains took place after training. A split-plot ANOVA was used in order to evaluate the interaction between Time (assessment phase) and the type of group (experimental vs. control), taking into account age, level of education and severity of lesion as covariates. Level of significance was chosen to be $p < 0.05$.

The fMRI data were analyzed using Brain Voyager QX Software (Brain Innovation, Maastricht, Holland). The functional data of each subject were pre-processed as follows: (1) Mean intensity adjustment in order to prevent global signal variability; (2) slice scan time correction, through the use of a sinc interpolation algorithm; (3) 3D motion correction: all the volumes were spatially aligned to the first volume by rigid body transformations, adopting a algorithm of trilinear interpolation; (4) spatial smoothing with a Gaussian kernel of 4 mm FWHM; and (5) temporal filters, i.e., linear and non-linear trend removal through the use of a temporal high-pass filter (frequency pass = 0.008 Hz), adopted to remove drifts due to scanner and other low frequency noises. After pre-processing, the temporal series of each voxel were filtered using a band-pass filter ($0.01 < f < 0.08$ Hz) in order to remove both the very low frequencies and the noise due to high frequencies (respiratory and cardiac frequencies). The filtered time series was then transformed into a frequency domain using Fourier transformation; this process allowed us to decompose a signal made up of several frequencies and identify the spectrum of the signal. The power spectrum represents the energy of the signal at different frequencies. Then a statistical analysis using the General Linear Model was performed to yield functional activation maps during the pre- and post-tests separately. Subsequently, the General Linear Model was used to compare post-test activations with pre-test activations for each participant. Statistical comparisons were computed at a statistical threshold of $p < 0.05$, corrected for multiple comparisons using Bonferroni correction, and a cluster threshold of 50 voxels.

RESULTS

The stimulation procedure was well tolerated by all the participants, who did not report any kind of problem during the tDCS administration.

Cognitive Performance

We conducted a paired samples T-test analysis on the DA subtest of the TEA. As expected, we observed no improvements due to the nonspecific control activities which the patients attended between T0 (baseline) and T1 (pre training), either in the experimental (RT: $t = 1.27$; $p = 0.22$; Omission Errors (OE): $t = 0.52$; $p = 0.61$) or in the control group (RT: $t = 0.45$; $p = 0.66$; OEs: $t = -0.44$; $p = 0.66$). Within the experimental group, patients' performance at T2 (post-training) was significantly better than at T1 (pre-training), with faster RTs ($t = 3.41$; $p = 0.004$) and fewer OEs ($t = 4.49$; $p < 0.0001$), and this improvement was stable 1 month after the end of the treatment (T2 vs. T3 RT: $t = 0.51$; $p = 0.62$; OEs: $t = 0.20$; $p = 0.84$). On the contrary, within the control group, patients' performance did not increase, either on RT ($t = -0.006$; $p = 0.99$) or on OEs ($t = 0.92$; $p = 0.37$).

At T0 and T3, we administered a series of neuropsychological tests to obtain a precise cognitive profile of the patients before and after the training program. As far as performance on the RBANS is concerned, within the experimental group the analysis did not reveal any statistically significant difference between performance before and after the training on visual-spatial abilities ($t = -0.670$; $p = 0.256$ one-tailed), semantic fluency ($t = 0.083$; $p = 0.467$), working memory ($t = -0.849$; $p = 0.204$), long-term memory ($t = -1.235$; $p = 0.118$); it showed, however, improved performance in the attention task, at the limits of statistical significance ($t = -1.679$; $p = 0.057$). Apathy scores showed significant improvement ($t = 1.793$; $p = 0.047$), while no relevant changes have been detected in the Depression scores ($t = 0.521$; $p = 0.305$).

A split-plot ANOVA with Time as the within subject factor (pre-training computed as the mean between T0 and T1 vs. post-training T2), Type of Group (Control vs. Experimental) as the between subject factor, and age, education level and severity of injury (Glasgow Coma Scale scores) as covariates was performed. It showed no interaction between Time and Age (RT: $F = 0.54$; $p = 0.47$; OEs: $F = 0.87$; $p = 0.36$), or between Time and Level of Education (RT: $F = 1.55$; $p = 0.22$; OEs: $F = 1.99$; $p = 0.17$). As far as the interaction between Time and Severity of injury is concerned, it was statistically significant for OEs ($F = 4.12$; $p = 0.05$), while it was insignificant for RT ($F = 0.51$; $p = 0.48$). As expected, a significant interaction emerged between Time and Type of Group (RT: $F = 4.13$; $p = 0.05$; OEs: $F = 5.12$; $p = 0.03$).

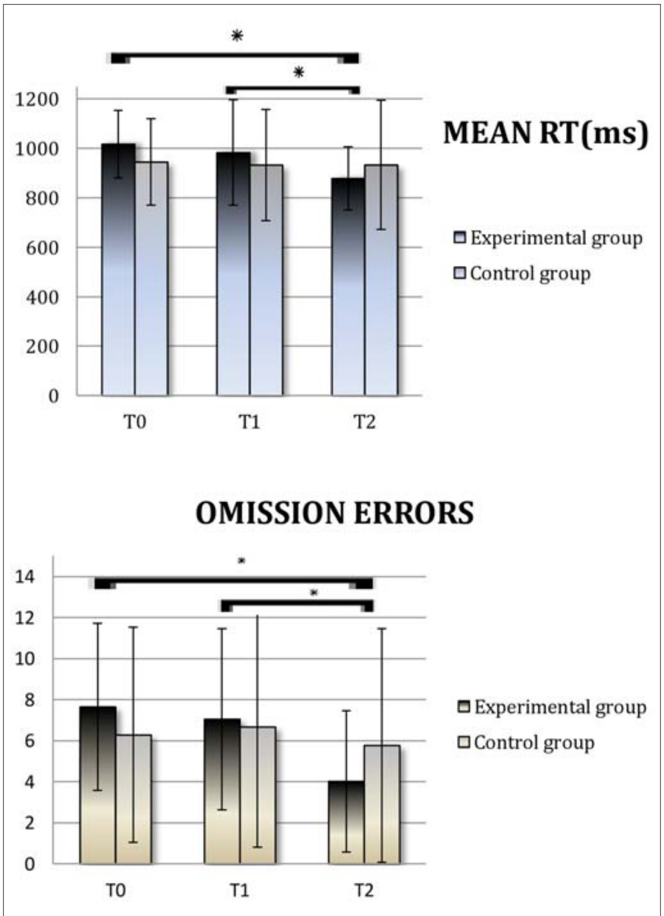


FIGURE 2 | Divided Attention (DA): Average scores obtained at T0 (Baseline), T1 (pre-Treatment) and T2 (post-Treatment) by the experimental group and the control group. Reaction time (RT) is expressed in milliseconds. RT; OE, Omission Errors. Asterisks indicate when the difference between performances is statistically significant.

Finally, an independent-sample t-test let us exclude that the Type of Montage had an effect on the improvements from pre- to post- training (RT: $t = 0.098$; $p = 0.923$; OE: $t = 1.218$; $p = 0.243$). The main results are represented in **Figure 2**.

Brain Activations

In the pre-treatment, the DA conditions (vs. rest conditions) analysis resulted in two clusters of activation. The first cluster includes extended portions of the following brain areas bilaterally: the inferior parietal lobule, the pre- and post-central gyri, the inferior, middle and medial frontal gyrus, the cingulate gyrus, the superior temporal gyrus, and the insula. The second cluster includes the right inferior occipital gyrus and the cerebellar declive and culmen bilaterally, see **Figure 3**.

The contrast of the DA conditions vs. the selective attention conditions (auditory + visual) resulted in a cluster of activation including the right posterior cingulate and right lingual gyrus, as well as the cuneus, precuneus and cingulate gyri bilaterally.

The post vs. pre-treatment comparisons showed a post-treatment significant decrease of activation in the right superior temporal gyrus, the middle frontal gyrus and the postcentral gyrus, as well as in the left middle and inferior frontal gyri, see **Figure 4**. The contrast of the DA conditions vs. the selective attention conditions, in the post minus pre-treatment comparisons, resulted in a decrease of activation in a small portion of the right cingulate gyrus (Talairach cordinates: 5; −38; 33).

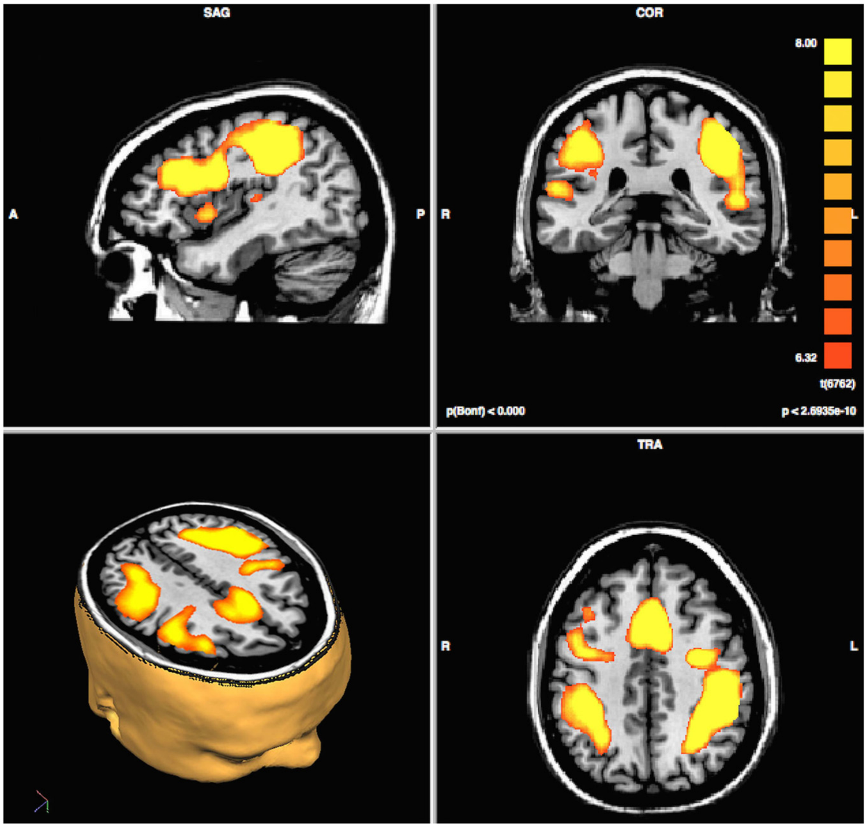
DISCUSSION

The purpose of this study was to investigate the role of combined tDCS and computer-based training on DA performance following severe TBI. Indeed, given that there is limited evidence of the effectiveness of standard rehabilitation programs aimed at improving attention, especially when chronic patients are involved, this study was intended to explore whether brain stimulation—favoring neuroplastic changes—may enhance the effects of a cognitive training.

Overall, the findings support the idea that 1 week of intensive rehabilitation associated with neuromodulation techniques could significantly contribute to the enhancement of attentional abilities even in chronic patients with a stabilized cognitive profile. Indeed, when performing the DA task, the experimental group obtained significantly better results after the treatment than in the two previous assessments. Furthermore, this improvement was maintained in the follow-up evaluation, performed 1 month after the end of the treatment, highlighting its long-lasting effects. On the contrary, the control group showed no significant improvement. The difference between the experimental and the control group confirmed the efficacy of the combined treatment, as the computerized training alone is not sufficient to produce a significant change on TBI participants' performance. Among other variables, the severity of the lesion seems to affect the quality, even if not the speed, of performance.

It is worth considering that the improvement concerned attention abilities and was not generalized across other cognitive abilities. Participants belonging to the experimental group showed improved performance in the attention task of the RBANS battery, but not in any other cognitive domain. On this basis, we can conclude that the treatment had specific effects on DA, an outcome which is similar to that reported by Couillet et al. (2010), whose training only ameliorated the ability to complete two tasks simultaneously, without having effects on other cognitive functions.

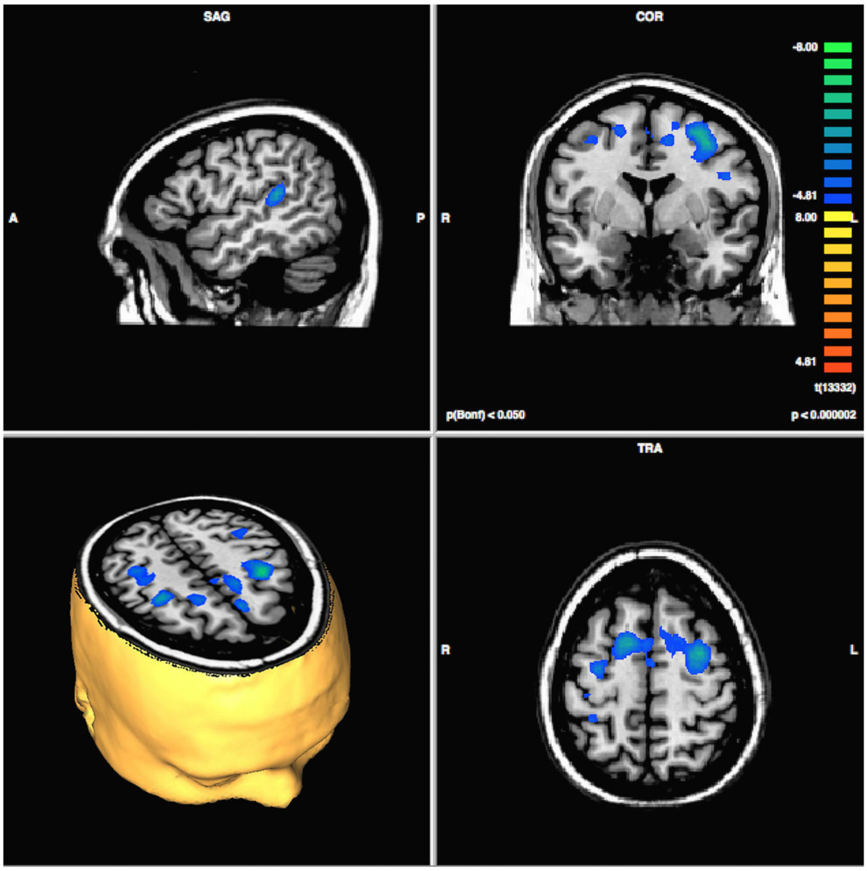
Some previous works investigated the effect of tDCS over the DLPFC in subacute and chronic TBI patients, but results are not clear-cut. A first pilot study (Kang et al., 2012) explored the effect of a single tDCS session: improvements in RT during an attention task were found immediately post-stimulation, but were not significant after 3 or 24 h. Park et al. (2013) investigated the effectiveness of repeated tDCS sessions associated with a computerized training on attention and memory in a small group of stroke patients, showing post-training improvements of performance. Ulam et al. (2015) studied the cumulative effects of tDCS on electroencephalographic (EEG) oscillations,



Localization	*Local maxima: Talairach coordinates (x; y; z)*	*t*
Left Inferior Parietal Lobule	−40; −34; 39	1.556
Bilat Inferior Parietal Lobule		
Bilat Precentral Gyrus		
Bilat Postcentral Gyrus		
Bilat Inferior Frontal Gyrus		
Bilat Middle Frontal Gyrus		
Bilat Medial Frontal Gyrus		
Bilat Cingulate Gyrus		
Bilat Superior Temporal Gyrus		
Bilat Insula		
Right Inferior Occipital Gyrus		
Bilat Declive	29; −92; −3	8.801
Bilat Culmen		

FIGURE 3 | Results of pre-treatment functional magnetic resonance imaging (fMRI) analysis ($N = 11$; $p < 2.3965e^{-10}$).

showing significant modifications correlated with improved performance on attention and working memory tests. On the contrary, the results of another study (Leśniak et al., 2014) did not provide sufficient evidence to support the efficacy of a 15-day rehabilitation training program preceded by tDCS. One possibility is that such contradictory results are due to the utilization of an undifferentiated protocol for all patients, irrespective of the lesion site. Many authors (e.g., Brunoni et al., 2012; Villamar et al., 2012) have pointed out the importance of personalizing the locations of electrodes, especially with brain-damaged subjects. This is particularly relevant when working with TBI patients, given the heterogeneity of their clinical picture and anatomical and functional damage. It is fair to say that some authors (Asloun et al., 2008; Bikson et al., 2010) have claimed that electrode montage has a critical role in modifying the amount of current shunted through the cortex. Indeed, computational modeling studies have predicted that a different position of the return electrode may influence the



Localization	*Local maxima: Talairach coordinates (x; y; z)*	*t*
Right Superior Temporal Gyrus	53; −29; 12	−6.801
Right Middle Frontal Gyrus	32; −8; 45	−6.802
Right Postcentral Gyrus	32; −26; 45	−5.797
Left Middle Frontal Gyrus	−31; 1; 48	−7.848
Left Inferior Frontal Gyrus	−46; −2; 24	−6.231

FIGURE 4 | Results of post-minus pre-treatment fMRI analysis ($N = 11$; $p < 0.000002$).

total current flow produced by the stimulating electrode (Bikson et al., 2010); as a consequence, a change in the return electrode position may influence the current flow under the target region stimulated by the other electrode. However, other modeling studies have shown that, when considering TBI patients, other variables, such as anatomical differences, defects and lesions in the brain—i.e., the presence of cerebrospinal fluid—are expected to distort current flow (Bikson et al., 2012). All these reasons considered, we chose to locate the electrodes according to each participant's specific damage. This personalized electrode location might have facilitated a more functional network restoration.

Besides the behavioral improvement, our study showed brain modifications: the fMRI assessment seems to suggest a more functional and specific neural organization post-treatment. Indeed, our main fMRI result consists in a decrease in cerebral activations during the DA condition post-treatment. This is in line with the previous literature, reporting significant hyperactivations in patients with TBI performing dual tasks (Rasmussen et al., 2008; Sozda et al., 2011). In particular, Rasmussen et al. (2008) recounted significantly higher activation of a prefrontal-anterior midline-parietal network in TBI subjects in the dual-task condition compared to the matched controls. These regions have been described as being engaged in healthy volunteers as the cost of dual tasking increases (e.g., Herath et al., 2001; Collette et al., 2005). Thus, it seems that, following TBI, there is a functional reorganization within the primary network subserving the task, demonstrating more effortful processing. The authors also claimed that recruitment of these additional cortical resources may be connected to serial rather than parallel processing in low-level dual tasking in TBI patients and thus, that in patients with severe TBI low-level dual task performance may depend on increased attentional and executive guidance. Following this line of reasoning, it is not surprising that the combined tDCS and cognitive training were accompanied by a decrease in cerebral activations: this can be interpreted as normalization of previously abnormal hyperactivations. More specifically, such a decrease concerns a network of areas, including the left DLPFC, the bilateral premotor and supplementary motor areas, the right parietal somatosensory cortex and the right auditory processing cortex. These areas have been found to be involved in dual task processing in healthy subjects (Loose et al., 2003; Nebel et al., 2005; Tachibana et al., 2012), as they subserve the allocation of attention, reflecting the higher executive demand required in divided vs. selective attention tasks. In particular, Johnson et al. (2007) interpreted the increase of activity in DLPFC during DA tasks as reflecting manipulation of information in working memory. According to the authors, when the activity of these areas is temporarily inhibited by slow rTMS, the ability to maintain multiple pieces of information in working memory is also compromised, thus leading to a failure in performing DA tasks.

In conclusion, the proposed treatment resulted in a significant improvement in DA, which was maintained over a long period of time. The combined use of tDCS and computer-based training appears to have favored a neural reorganization, diminishing the patients' cognitive effort. However, our study presents some limitations. First, the limited number of patients prevented us from performing a subgroup analysis according to the different tDCS electrodes' montage. Secondly, although patients were in the chronic phase of their injury and their neurological profile was stable, a baseline fMRI test would have helped in better understanding the cerebral mechanisms that accompany the cognitive improvement. Finally, this experiment was aimed at detecting the combined effect of cognitive training and tDCS: future studies involving specific trials aimed at testing the efficacy of the two interventions separately would be very useful in separating the role of each variable.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct and intellectual contributions to the work, and approved it for publication.

ACKNOWLEDGMENTS

This research has been supported by local research funds (ex 60%) managed by University of Turin, Department of Psychology, year 2014, and by the *Brain Imaging Group* Association. The authors are grateful to the patients who participated in the research, and to the reviewers. A special thanks goes to our radiology technician, Dumitru Scafesi, for his courtesy and kindness.

REFERENCES

Andelic, N., Hammergren, N., Bautz-Holter, E., Sveen, U., Brunborg, C., and Røe, C. (2009). Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. *Acta Neurol. Scand.* 120, 16–23. doi: 10.1111/j.1600-0404.2008.01116.x

Asloun, S., Soury, S., Couillet, J., Giroire, J. M., Joseph, P. A., Mazaux, J. M., et al. (2008). Interactions between divided attention and working-memory load in patients with severe traumatic brain injury. *J. Clin. Exp. Neuropsychol.* 30, 481–490. doi: 10.1080/13803390701550144

Azouvi, P., Couillet, J., Leclercq, M., Martin, Y., Asloun, S., and Rousseaux, M. (2004). Divided attention and mental effort after severe traumatic brain injury. *Neuropsychologia* 42, 1260–1268. doi: 10.1016/j.neuropsychologia.2004.01.001

Beck, A. T., Ward, C. H., Mendelson, M. D., Mock, J., and Erbaugh, J. (1961). Beck depression inventory (BDI). *Arch. Gen. Psychiatry* 4, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Bikson, M., Datta, A., Rahman, A., and Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. *Clin. Neurophysiol.* 121, 1976–1978. doi: 10.1016/j.clinph.2010.05.020

Bikson, M., Rahman, A., Datta, A., Fregni, F., and Merabet, L. (2012). High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. *Neuromodulation* 15, 306–315. doi: 10.1111/j.1525-1403.2012.00481.x

Brouwer, W., Verzendaal, M., van der Naalt, J., Smit, J., and van Zomeren, E. (2001). Divided attention years after severe closed head injury: the effect of dependencies between the subtasks. *Brain Cogn.* 46, 54–56. doi: 10.1016/s0278-2626(01)80033-6

Brouwer, W. H., Withaar, F. K., Tant, M. L., and van Zomeren, A. H. (2002). Attention and driving in traumatic brain injury: a question of coping with time-pressure. *J. Head Trauma Rehabil.* 17, 1–15. doi: 10.1097/00001199-200202000-00003

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5, 175–195. doi: 10.1016/j.brs.2011.03.002

Cernich, A. N., Kurtz, S. M., Mordecai, K. L., and Ryan, P. B. (2010). Cognitive rehabilitation in traumatic brain injury. *Curr. Treat. Options Neurol.* 12, 412–423. doi: 10.1007/s11940-010-0085-6

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., et al. (2011). Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Arch. Phys. Med. Rehabil.* 92, 519–530. doi: 10.1016/j.apmr.2010.11.015

Clark, V. P., and Parasuraman, R. (2014). Neuroenhancement: enhancing brain and mind in health and in disease. *Neuroimage* 85, 889–894. doi: 10.1016/j.neuroimage.2013.08.071

Collette, F., Olivier, L., Van der Linden, M., Laureys, S., Delfiore, G., Luxen, A., et al. (2005). Involvement of both prefrontal and inferior parietal cortex in dual-task performance. *Brain Res. Cogn. Brain Res.* 24, 237–251. doi: 10.1016/j.cogbrainres.2005.01.023

Couillet, J., Soury, S., Lebornec, G., Asloun, S., Joseph, P. A., Mazaux, J. M., et al. (2010). Rehabilitation of divided attention after severe traumatic brain injury: a randomised trial. *Neuropsychol. Rehabil.* 20, 321–339. doi: 10.1080/09602010903467746

Cyr, A. A., Stinchcombe, A., Gagnon, S., Marshall, S., Hing, M. M., and Finestone, H. (2009). Driving difficulties of brain-injured drivers in reaction to high-crash-risk simulated road events: a question of impaired divided attention? *J. Clin. Exp. Neuropsychol.* 31, 472–482. doi: 10.1080/13803390802255627

De Luca, R., Calabrò, R. S., Gervasi, G., De Salvo, S., Bonanno, L., Corallo, F., et al. (2014). Is computer-assisted training effective in improving rehabilitative outcomes after brain injury? A case-control hospital-based study. *Disabil. Health J.* 7, 356–360. doi: 10.1016/j.dhjo.2014.04.003

De Renzi, E., and Vignolo, L. A. (1962). The token test: a sensitive test to detect receptive disturbances in aphasics. *Brain* 85, 665–678. doi: 10.1093/brain/85.4.665

Flöel, A. (2014). tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage* 85, 934–947. doi: 10.1016/j.neuroimage.2013.05.098

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Herath, P., Klingberg, T., Young, J., Amunts, K., and Roland, P. (2001). Neural correlates of dual task interference can be dissociated from those of divided attention: an fMRI study. *Cereb. Cortex* 11, 796–805. doi: 10.1093/cercor/11.9.796

Jackson, M. L., Hughes, M. E., Croft, R. J., Howard, M. E., Crewther, D., Kennedy, G. A., et al. (2011). The effect of sleep deprivation on BOLD activity elicited by a divided attention task. *Brain Imaging Behav.* 5, 97–108. doi: 10.1007/s11682-011-9115-6

Johnson, J. A., Strafella, A. P., and Zatorre, R. J. (2007). The role of the dorsolateral prefrontal cortex in bimodal divided attention: two transcranial magnetic stimulation studies. *J. Cogn. Neurosci.* 19, 907–920. doi: 10.1162/jocn.2007.19.6.907

Johnson, J. A., and Zatorre, R. J. (2005). Attention to simultaneous unrelated auditory and visual events: behavioral and neural correlates. *Cereb. Cortex* 15, 1609–1620. doi: 10.1093/cercor/bhi039

Johnson, J. A., and Zatorre, R. J. (2006). Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. *Neuroimage* 31, 1673–1681. doi: 10.1016/j.neuroimage.2006.02.026

Kang, E. K., Kim, D. Y., and Paik, N. J. (2012). Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. *J. Rehabil. Med.* 44, 346–350. doi: 10.2340/16501977-0947

Klingberg, T. (2000). Limitations in information processing in the human brain: neuroimaging of dual task performance and working memory tasks. *Prog. Brain Res.* 126, 95–102. doi: 10.1016/s0079-6123(00)26009-3

Leclercq, M., and Azouvi, P. (2002). "Attention after traumatic brain injury," in *Applied Neuropsychology of Attention: Theory Diagnosis, and Rehabilitation*, eds M. Leclercq and P. Zimmermann (New York, NY: Psychology Press), 257–279.

Leśniak, M., Polanowska, K., Seniów, J., and Członkowska, A. (2014). Effects of repeated anodal tDCS coupled with cognitive training for patients with severe traumatic brain injury: a pilot randomized controlled trial. *J. Head Trauma Rehabil.* 29, E20–E29. doi: 10.1097/HTR.0b013e318292a4c2

Loose, R., Kaufmann, C., Auer, D. P., and Lange, K. W. (2003). Human prefrontal and sensory cortical activity during divided attention tasks. *Hum. Brain Mapp.* 18, 249–259. doi: 10.1002/hbm.10082

Marin, R. S., Biedrzycki, R. C., and Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Res.* 38, 143–162. doi: 10.1016/0165-1781(91)90040-v

Masson, M., Michael, G. A., Désert, J. F., Rhein, F., Foubert, L., and Colliot, P. (2013). Specific attention disorders in drivers with traumatic brain injury. *Brain Inj.* 27, 538–547. doi: 10.3109/02699052.2013.766926

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., et al. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimul.* 1, 326–336. doi: 10.1016/j.brs.2008.07.002

Montani, V., De Filippo De Grazia, M., and Zorzi, M. (2014). A new adaptive videogame for training attention and executive functions: design principles and initial validation. *Front. Psychol.* 5:409. doi: 10.3389/fpsyg.2014.00409

Nebel, K., Wiese, H., Stude, P., de Greiff, A., Diener, H. C., and Keidel, M. (2005). On the neural basis of focused and divided attention. *Brain Res. Cogn. Brain Res.* 25, 760–776. doi: 10.1016/j.cogbrainres.2005.09.011

Park, S. H., Koh, E. J., Choi, H. Y., and Ko, M. H. (2013). A double-blind, sham-controlled, pilot study to assess the effects of the concomitant use of transcranial direct current stimulation with the computer assisted cognitive rehabilitation to the prefrontal cortex on cognitive functions in patients with stroke. *J. Korean Neurosurg. Soc.* 54, 484–488. doi: 10.3340/jkns.2013.54.6.484

Park, N. W., Moscovitch, M., and Robertson, I. H. (1999). Divided attention impairments after traumatic brain injury. *Neuropsychologia* 37, 1119–1133. doi: 10.1016/s0028-3932(99)00034-2

Ponsford, A., and Clements, R. (1991). A modified view of the facial bones in the seriously injured. *Radiogr. Today* 57, 10–12.

Poreisz, C., Boros, K., Antal, A., and Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res. Bull.* 72, 208–214. doi: 10.1016/j.brainresbull.2007.01.004

Randolph, C., Tierney, M. C., Mohr, E., and Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological Status (RBANS): preliminary clinical validity. *J. Clin. Exp. Neuropsychol.* 20, 310–319. doi: 10.1076/jcen.20.3.310.823

Rasmussen, I. A., Xu, J., Antonsen, I. K., Brunner, J., Skandsen, T., Axelson, D. E., et al. (2008). Simple dual tasking recruits prefrontal cortices in chronic severe traumatic brain injury patients, but not in controls. *J. Neurotrauma* 25, 1057–1070. doi: 10.1089/neu.2008.0520

Scelzo, E., Ferrucci, R., Bortolomasi, M., Giacopuzzi, M., and Priori, A. (2011). Transcranial direct current stimulation (TDCS) for severe drug resistent major depression: a ten days treatment protocol. *Eur. Psychiatry* 26:1154. doi: 10.1016/s0924-9338(11)72859-0

Schulz, R., Gerloff, C., and Hummel, F. C. (2013). Non-invasive brain stimulation in neurological diseases. *Neuropharmacology* 64, 579–587. doi: 10.1016/j.neuropharm.2012.05.016

Serino, A., Ciaramelli, E., Santantonio, A. D., Malagù, S., Servadei, F., and Làdavas, E. (2007). A pilot study for rehabilitation of central executive deficits after traumatic brain injury. *Brain Inj.* 21, 11–19. doi: 10.1080/02699050601151811

Shin, Y. I., Foerster, A., and Nitsche, M. A. (2015). Transcranial direct current stimulation (tDCS) - Application in neuropsychology. *Neuropsychologia* 69, 154–175. doi: 10.1016/j.neuropsychologia.2015.02.002

Sozda, C. N., Larson, M. J., Kaufman, D. A., Schmalfuss, I. M., and Perlstein, W. M. (2011). Error-related processing following severe traumatic brain injury: an event-related functional magnetic resonance imaging (fMRI) study. *Int. J. Psychophysiol.* 82, 97–106. doi: 10.1016/j.ijpsycho.2011.06.019

Tachibana, A., Noah, J. A., Bronner, S., Ono, Y., Hirano, Y., Niwa, M., et al. (2012). Activation of dorsolateral prefrontal cortex in a dual neuropsychological screening test: an fMRI approach. *Behav. Brain Funct.* 8:26. doi: 10.1186/1744-9081-8-26

Toyokura, M., Nishimura, Y., Akutsu, I., Mizuno, R., and Watanabe, F. (2012). Selective deficit of divided attention following traumatic brain injury: case reports. *Tokai J. Exp. Clin. Med.* 37, 19–24.

Ulam, F., Shelton, C., Richards, L., Davis, L., Hunter, B., Fregni, F., et al. (2015). Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. *Clin. Neurophysiol.* 126, 486–496. doi: 10.1016/j.clinph.2014.05.015

van Zomeren, A., and van den Burg, W. (1985). Residual complaints of patients two years after severe head injury. *J. Neurol. Neurosurg. Psychiatry* 48, 21–28. doi: 10.1136/jnnp.48.1.21

Villamar, M. F., Santos Portilla, A., Fregni, F., and Zafonte, R. (2012). Noninvasive brain stimulation to modulate neuroplasticity in traumatic brain injury. *Neuromodulation* 15, 326–338. doi: 10.1111/j.1525-1403.2012.00474.x

Wagner, M., Rihs, T. A., Mosimann, U. P., Fisch, H. U., and Schlaepfer, T. E. (2006). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex affects divided attention immediately after cessation of stimulation. *J. Psychiatr. Res.* 40, 315–321. doi: 10.1016/j.jpsychires.2005.06.001

Withaar, F. K., Brouwer, W. H., and van Zomeren, A. H. (2000). Fitness to drive in older drivers with cognitive impairment. *J. Int. Neuropsychol. Soc.* 6, 480–490. doi: 10.1017/s1355617700644065

Zimmermann, P., and Fimm, B. (2002). "A test battery for attentional performance," in *Applied Neurophyschology of Attention: Theory, Diagnosis and Rehabilitation*, eds M. Leclercq, and P. Zimmerman (London: Psychology Press), 110–151.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read, for greatest visibility

COLLABORATIVE PEER-REVIEW
Designed to be rigorous – yet also collaborative, fair and constructive

FAST PUBLICATION
Average 85 days from submission to publication (across all journals)

COPYRIGHT TO AUTHORS
No limit to article distribution and re-use

TRANSPARENT
Editors and reviewers acknowledged by name on published articles

SUPPORT
By our Swiss-based editorial team

IMPACT METRICS
Advanced metrics track your article's impact

GLOBAL SPREAD
5'100'000+ monthly article views and downloads

LOOP RESEARCH NETWORK
Our network increases readership for your article

Frontiers
EPFL Innovation Park, Building I • 1015 Lausanne • Switzerland
Tel +41 21 510 17 00 • Fax +41 21 510 17 01 • info@frontiersin.org
www.frontiersin.org

Find us on