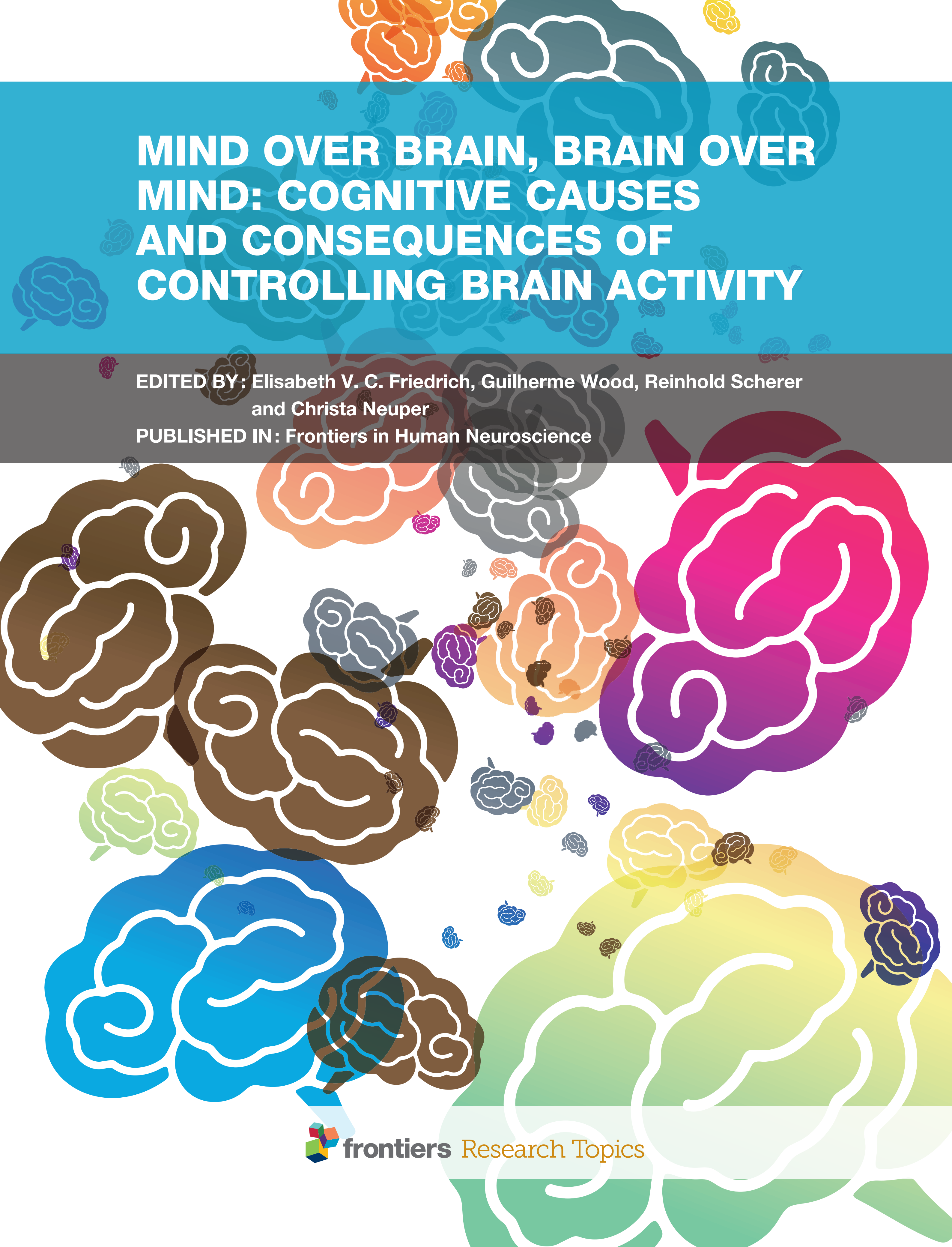

MIND OVER BRAIN, BRAIN OVER MIND: COGNITIVE CAUSES AND CONSEQUENCES OF CONTROLLING BRAIN ACTIVITY

EDITED BY: Elisabeth V. C. Friedrich, Guilherme Wood, Reinhold Scherer
and Christa Neuper
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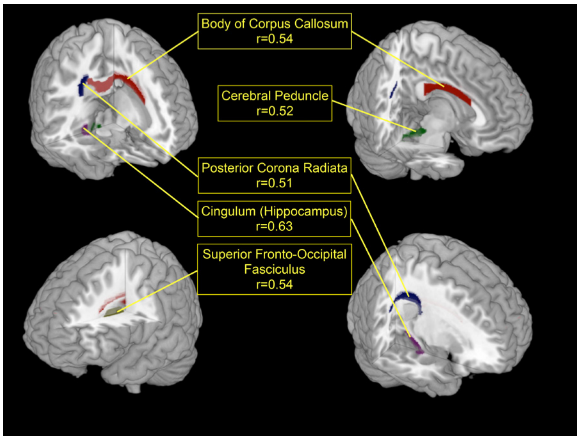
MIND OVER BRAIN, BRAIN OVER MIND: COGNITIVE CAUSES AND CONSEQUENCES OF CONTROLLING BRAIN ACTIVITY

Topic Editors:
Elisabeth V. C. Friedrich, University of Graz, BioTechMed-Graz, Austria
Guilherme Wood, University of Graz, BioTechMed-Graz, Graz, Austria
Reinhold Scherer, Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, BioTechMed-Graz, Austria
Christa Neuper, University of Graz, BioTechMed-Graz, Austria



Structural brain traits correlate with individual brain-computer interface performance.
Image taken from: Halder S, Varkuti B, Bogdan M, Kübler A, Rosenstiel W, Sitaram R and Birbaumer N (2013) Prediction of brain-computer interface aptitude from individual brain structure. Front. Hum. Neurosci. 7:105. doi: 10.3389/fnhum.2013.00105

This Research Topic combines articles aiming to gain a better understanding on different factors that determine whether people are successful or not in controlling computerized devices with brain signals. Since decades, technological advancements in neuroscience allow the interpretation of brain signals and their translation into control messages (Brain-computer interface (BCI)). Moreover, the control of brain signals can be used to induce changes in cognition and behavior (Neurofeedback (NF)). However, the break-through of this technology for the broad population in real-world applications has not yet arrived.

Various factors have been related to the individual success in controlling computerized devices with brain signals, but to date, no general theoretical framework is available. In this Research Topic, aspects of the training protocol such as instructions, task and feedback as well as cognitive and psychological traits such as motivation, mood, locus of control and empathy are investigated as determinants of BCI or NF performance. Moreover, the mechanisms and networks involved in gaining and maintaining control over brain activity as well as its prediction are addressed. Finally, as the ultimate goal of this research is to use BCI and NF for communication or control and therapy, respectively, novel applications for individuals with disabilities or disorders are discussed.

The first part of the Research Topic deals with the role of the training protocol in BCI and NF. In the hypothesis and theory article of Lotte and colleagues, problems in current BCI training protocols are identified according to instructional design principles. Solutions for improving instruction, task and feedback are also proposed. Kober and colleagues report that participants who stop employing a specific mental strategy during the course of NF training show increased performance in an electroencephalographic (EEG)-based NF training paradigm controlled by modulation of the sensorimotor rhythm (SMR).

The findings addressing the impact of psychological traits on performance are in line with the above presented results. Subramaniam and Vinogradov discuss in their review article how positive mood states change brain patterns and improve cognitive performance, which implies that mood states might also influence BCI and NF performance. Moreover, motivation and personality traits might also change brain patterns and performance. In contrast to earlier findings, Kleih and Kuebler do not find a correlation between motivation and performance in an EEG-based P300-BCI. However, these authors report a negative correlation of empathic characteristics and P300 amplitudes. Also, Witte and colleagues found a negative correlation between the locus of control with regard to technology and SMR power in an EEG-based SMR-NF. The authors of both articles conclude that a high degree of empathy as well as high expectations regarding the locus of control might lead to emotional or cognitive overload, which, in turn, leads to lower performance in P300 or SMR-based BCIs. This is in line with the findings of Kober and colleagues addressing spontaneous mental tasks. Thus, a state of positive but not emotionally involved attentive and effortless relaxation might be the optimal state to control both NF and BCI.

Besides external and internal factors influencing performance, neurophysiological as well as peripheral physiological correlates of gaining and maintaining control of brain activity are important to address. Ninaus and colleagues found in their study using functional magnetic resonance imaging (fMRI) that the fronto-parietal and cingulo-opercular network, which is typically involved in cognitive control, is also active when participants believe to control a NF but in reality get sham feedback. Thus, the intention of control is sufficient to activate networks usually engaged in cognitive control. Berman and colleagues examine the possibility to control brain activity within a functionally localized region of the anterior right insular cortex with fMRI-based NF. Also, peripheral physiological signals might have an impact on cognitive control. Pfurtscheller and colleagues investigate the interaction between brain and heart and suggested that the changes in heart rate in correlation with motor imagery can be used as indicator of mental effort to improve BCI control.

To predict the ability to control a NF or BCI, Halder and colleagues performed MRI scans after one session of EEG-based SMR-BCI using motor imagery and report a positive correlation between individual BCI performance and the structural integrity and myelination quality of deep white matter structures. Also using MRI scans, Enriquez-Geppert and colleagues show that the volume of the midcingulate cortex as well as volume and concentration of the underlying white matter structures predicts EEG-based NF performance of frontal-midline theta performance. Both studies indicate that there is a neuroanatomical foundation for the aptitude to control a BCI or NF. In contrast to the above research studies, Riccio and colleagues investigate predictor variables of performance in an EEG-based P300-BCI in individuals with amyotrophic lateral sclerosis. They conclude that the temporal filtering capacity (i.e. ability to keep the attentional filter active during target selection) is crucial for BCI control.

The last part covers potential applications for individuals with disabilities or mental disorders. Risetti and colleagues present findings of an EEG-based P300 auditory oddball paradigm to investigate residual unconscious and conscious cognitive function in individuals with a disorder of consciousness. Micoulaud and colleagues propose in their perspective article to couple repetitive transcranial magnetic stimulation (rTMS) with NF and discuss therapeutic implications and ethical issues.

In summary, this Research Topic provides novel evidence on how different factors impact on BCI and NF performance based mainly on electrophysiological and neuroimaging research including able-bodied as well as disabled populations. Moreover, new perspectives that need addressing in the future are outlined.

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Mind over brain, brain over mind: cognitive causes and consequences of controlling brain activity

Elisabeth V. C. Friedrich[1,2]*, Guilherme Wood[1], Reinhold Scherer[3] and Christa Neuper[1,3]

[1] *Department of Psychology, University of Graz, BioTechMed-Graz, Graz, Austria*
[2] *Department of Cognitive Science, University of California San Diego, La Jolla, CA, USA*
[3] *Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, BioTechMed-Graz, Graz, Austria*
**Correspondence: efriedrich@ucsd.edu*

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John J. Foxe, Albert Einstein College of Medicine, USA

Keywords: brain-computer interface (BCI), neurofeedback (NF), electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), training protocol, psychological traits, control and its prediction, applications for disabled individuals

Brain activity is considered the physical correlate of mental activity. Accordingly, a change of the state of mind implies a change in the state of the brain and vice versa. This homology between brain activity and cognitive tasks is very difficult to measure due to their very high complexity, temporal and spatial dynamics, as well as individual variability. However, the advancing of technology allows the detection of some states of brain activity with reasonable accuracy and their translation into control messages for devices external to the brain (i.e., brain-computer-interfaces, BCI). Moreover, studies on neurofeedback (NF) show that individuals can learn to modulate their own brain activity based on external feedback and thereby induce changes in cognition and behavior which can be used as therapy for various mental disorders.

Interestingly, roughly about one third of people succeed in controlling computerized devices with brain signals right away; one third gains control after training and one third does not achieve useful control even by using state-of-the-art BCI or NF technology. Various factors have been related to the individual success but to date, no general theoretical framework is available. In this Research Topic, **aspects of the training protocol** such as instructions, task and feedback as well as **psychological traits** such as motivation, mood, locus of control, and empathy are investigated as determinants of BCI or NF performance. Moreover, the brain generates a large amount of coherent spontaneous activity independently of the BCI or NF task at hand which negatively impacts the reliable detection of brain activity patterns. Thus, the mechanisms and networks involved in gaining and maintaining **control over brain activity** as well as **its prediction** are addressed. Finally, as the ultimate goal of our research is to use BCI and NF for communication or control and therapy, respectively, novel **applications for individuals with disabilities or disorders** are discussed.

The first part of the research topic deals with the role of **the training protocol** in BCI and NF. In the hypothesis and theory article of Lotte et al. (2013), problems in current BCI training protocols are identified according to instructional design principles and solutions for improved instruction, task, and feedback are proposed. Kober et al. (2013) report that the failure to describe a specific mental strategy when learning NF is indicative of better performance in an electroencephalographic (EEG)-based NF training paradigm controlled by modulation of the sensorimotor rhythm (SMR). Addressing the impact of the feedback in EEG-based BCIs, Koerner et al. (2014) demonstrate that the presentation of sham positive feedback resulted in different and better classifiable EEG patterns in comparison to sham negative feedback. Thus, the feedback success rate directly influences brain signals.

The findings addressing the impact of **psychological traits** on performance are in line with the above presented results. Subramaniam and Vinogradov (2013) discuss in their review article how positive mood states change brain patterns and improve cognitive performance, which implies that mood states might also influence BCI and NF performance. Moreover, motivation and personality traits might also change brain patterns and performance. In contrast to earlier findings, Kleih and Kübler (2013) do not find a correlation between motivation and performance in an EEG-based P300-BCI. However, these authors report a negative correlation of empathic characteristics and P300 amplitudes. Also, Witte et al. (2013) demonstrate a negative correlation between the locus of control with regard to technology and SMR power in an EEG-based SMR-NF. The authors of both articles conclude that a high degree of empathy as well as high expectations regarding the locus of control might lead to emotional or cognitive overload, which, in turn, leads to lower performance in P300 or SMR-based BCIs. This is in line with the findings of Kober and colleagues addressing spontaneous mental tasks. Thus, a state of positive but not emotionally involved attentive and effortless relaxation might be the optimal state to control both NF and BCI.

Besides external and internal factors influencing performance, neurophysiological as well as peripheral physiological correlates of gaining and maintaining **control of brain activity** are important to address. Ninaus et al. (2013) demonstrate in their study using functional magnetic resonance imaging (fMRI) that the fronto-parietal and cingulo-opercular network which are typically involved in cognitive control is active when participants believe to control a NF. Berman et al. (2013) examine the possibility to control the functionally localized anterior right insular cortex with fMRI-based NF. Also, peripheral physiological signals might have an impact on cognitive control. Pfurtscheller et al. (2013) investigate the interaction between brain and heart and suggest that the changes in heart rate in correlation with motor imagery can be used as indicator of mental effort to improve BCI control.

To **predict the ability to control** a NF or BCI, Halder et al. (2013) performed MRI scans after one session of EEG-based SMR-BCI using motor imagery and report a positive correlation between individual BCI performance and the structural integrity and myelination quality of deep white matter structures. Also using MRI scans, Enriquez-Geppert et al. (2013) show that the volume of the midcingulate cortex as well as volume and concentration of the underlying white matter structures predicts EEG-based NF performance of frontal-midline theta performance. Both studies indicate that there is a neuroanatomical foundation for the aptitude to control a BCI or NF. In contrast to all mentioned research studies so far, Riccio et al. (2013) included individuals with amyotrophic lateral sclerosis to investigate predictor variables of performance in an EEG-based P300-BCI. They conclude that the temporal filtering capacity (i.e., ability to keep the attentional filter active during target selection) is crucial for BCI control.

The last part covers potential **applications** for individuals with disabilities or mental disorders. Risetti et al. (2013) present findings of an EEG-based P300 auditory oddball paradigm to investigate residual unconscious and conscious cognitive function in individuals with a disorder of consciousness. Micoulaud-Franchi et al. (2013) propose in their perspective article to couple repetitive transcranial magnetic stimulation (rTMS) with NF and discuss therapeutic implications and ethical issues.

In summary, this Research Topic illustrates how different factors impact BCI and NF performance and provides new perspectives that need addressing in the future.

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Flaws in current human training protocols for spontaneous Brain-Computer Interfaces: lessons learned from instructional design

Fabien Lotte *, Florian Larrue and Christian Mühl

Inria Bordeaux Sud-Ouest/LaBRI, Talence, France

Edited by:
Reinhold Scherer, Graz University of Technology, Austria

Reviewed by:
Benjamin Blankertz, Technische Universität Berlin, Germany
Tobias Kaufmann, Julius-Maximilian University of Würzburg, Germany

****Correspondence:***
Fabien Lotte, Inria Bordeaux Sud-Ouest/LaBRI, 200 rue de la vieille tour, 33405 Talence Cedex, France
e-mail: fabien.lotte@inria.fr

While recent research on Brain-Computer Interfaces (BCI) has highlighted their potential for many applications, they remain barely used outside laboratories. The main reason is their lack of robustness. Indeed, with current BCI, mental state recognition is usually slow and often incorrect. Spontaneous BCI (i.e., mental imagery-based BCI) often rely on mutual learning efforts by the user and the machine, with BCI users learning to produce stable ElectroEncephaloGraphy (EEG) patterns (spontaneous BCI control being widely acknowledged as a skill) while the computer learns to automatically recognize these EEG patterns, using signal processing. Most research so far was focused on signal processing, mostly neglecting the human in the loop. However, how well the user masters the BCI skill is also a key element explaining BCI robustness. Indeed, if the user is not able to produce stable and distinct EEG patterns, then no signal processing algorithm would be able to recognize them. Unfortunately, despite the importance of BCI training protocols, they have been scarcely studied so far, and used mostly unchanged for years. In this paper, we advocate that current human training approaches for spontaneous BCI are most likely inappropriate. We notably study instructional design literature in order to identify the key requirements and guidelines for a successful training procedure that promotes a good and efficient skill learning. This literature study highlights that current spontaneous BCI user training procedures satisfy very few of these requirements and hence are likely to be suboptimal. We therefore identify the flaws in BCI training protocols according to instructional design principles, at several levels: in the instructions provided to the user, in the tasks he/she has to perform, and in the feedback provided. For each level, we propose new research directions that are theoretically expected to address some of these flaws and to help users learn the BCI skill more efficiently.

Keywords: Brain-Computer Interface, instructional design, electroencephalography, training protocols, feedback

1. INTRODUCTION

Brain-Computer Interfaces (BCI) are communication systems that enable users to send commands to a computer by using only their brain activity, this activity being generally measured using ElectroEncephaloGraphy (EEG) [see McFarland and Wolpaw (2011) for a review]. BCI have been shown to be very promising, notably for communication and control applications for severely disabled users (Wolpaw et al., 2002), but also in numerous other applications, such as rehabilitation (Pfurtscheller et al., 2008), human-computer interaction (Tan and Nijholt, 2010) or entertainment (Lécuyer et al., 2008), among many other (van Erp et al., 2012). Despite this potential, most BCI applications remain prototypes that are not used in practice, outside laboratories. The main reason is the widely acknowledged low reliability and low robustness of current BCI systems, especially as compared to alternative interfaces, e.g., computer mice or eye trackers. Indeed, the brain activity patterns produced by the user (e.g., resulting from imagining left hand movement to move a cursor toward the left) are too often incorrectly recognized by the BCI (McFarland and Wolpaw, 2011). These poor performances are due in part to the imperfect signal processing algorithms used to analyze and classify EEG signals. Indeed, these algorithms are not yet able to extract robustly the relevant information from EEG signals in the presence of various noise sources, signal non-stationarity and with limited amount of data available (McFarland and Wolpaw, 2011; van Erp et al., 2012). However, this is not the only reason that may explain such poor performance and reliability. In particular, there is another component of the BCI loop that may also be deficient: the user him/herself who may not be able to produce reliable EEG patterns (Allison and Neuper, 2010). Indeed, it is widely acknowledged that "BCI use is a skill" (Wolpaw et al., 2002), which means the user must be properly trained to be able to successfully use the BCI. Specifically, this is essential for BCI based on the recognition of mental imagery tasks (e.g., motor imagery, Neuper and Pfurtscheller, 2010), the so-called spontaneous BCI, which are the focus of this article[1]. If the user of a spontaneous BCI is indeed unable to correctly perform the desired mental commands, whatever the signal processing algorithms used, there would be no way to properly identify them. Despite this, the BCI community has focused the majority of its research efforts on signal processing and machine learning, mostly neglecting the human in the loop.

In this paper, we argue that the user is one of the most critical component of the BCI loop that may explain the limited reliability of current spontaneous BCI. It does not mean that BCI users are *per se* poor performers or incompetent. It means that the way current spontaneous BCI training protocols are designed is likely to be inappropriate, hindering BCI users to properly learn and use the BCI skill. Indeed, based on a careful analysis of feedback and instructional design literature, we have identified numerous flaws in the design of current spontaneous BCI training approaches. From an instructional design point of view, such flaws are known to impede successful skill learning and may thus explain the poor BCI performances or the fact that some people cannot use a BCI at all [the so-called "BCI illiteracy/inefficiency," which affects about 20% of BCI users (Allison and Neuper, 2010; Blankertz et al., 2010)].

In this paper, we therefore describe the flaws we have identified in the designs of spontaneous BCI training approaches. Moreover, for each of these flaws, we suggest new research directions that are theoretically expected to address it and, hopefully, to lead to a more efficient learning of the BCI skill. It should be stressed that these suggestions are only based on theory and their related hypotheses. As such, they are not proven solutions, and would require formal validation in the future. Nonetheless, we hope this paper will provoke discussions, debates and more works on this important area of BCI research.

This paper is organized as follows: the next section presents a state-of-the-art of human training approaches for spontaneous BCI. Then, the following section identifies the flaws in the design of these classic approaches based on instructional design literature, and suggest new directions to try to overcome them. More precisely, these flaws and suggestions are targeted at different levels of the training approaches (see also **Figure 1**): at the level of the feedback the user receives, at the level of the instructions provided to him/her, and finally at the level of the training tasks. The last section summarizes the identified flaws and corresponding suggestions and concludes the paper.

2. STATE-OF-THE-ART

Current spontaneous BCI training approaches are rather similar across different BCI designs, and have been mostly the same for years. There have been surprisingly few studies on the impact of various training approaches on BCI performances and user training, in particular as compared to the number of studies on EEG signal processing. Nevertheless, a few interesting research works on feedback and human training approaches have been conducted. This section first presents the common BCI training approaches currently used, then reviews research works that explored alternative approaches.

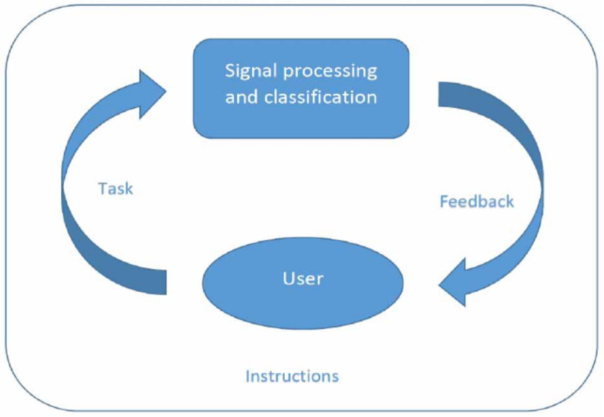

FIGURE 1 | Conventionally, BCI research is focused mostly on the signal processing and algorithms necessary to translate mental patterns into control commands. The user and the context in which he or she is learning to produce mental patterns is, on the other hand, often treated with neglect. We argue that the *tasks* a user has to perform, the *feedback* that informs about the performance, and the *instructions* that enable to perform are equally important and discuss them based on literature from instruction design.

2.1. CURRENT BCI TRAINING APPROACHES

BCI control being a skill, it has to be learned, refined and mastered by the BCI user. Neurofeedback[2] training has been proven to be a necessary component to learn the BCI skill (Neuper and Pfurtscheller, 2010). BCI neurofeedback training principles mostly depend on the type of BCI category used (Wolpaw et al., 2002):

- *The operant conditioning approach*, in which the EEG signal decoder/classifier is fixed and unknown to the user, and this user has to find out how to control a cursor by modulating his/her brain activity in a specific way. Using this kind of approach, the training can last for weeks or even months before the user can control the BCI. This was the approach used to successfully design the first BCI systems (Wolpaw et al., 1991; Birbaumer et al., 1999).
- *The machine learning approach*, in which the EEG decoder/classifier is optimized on examples of EEG signals collected from the user while he/she performs the targeted mental tasks. With this approach the training time before the user can control the BCI is much shorter (about 20 min for 2 classes), see, e.g., (Millán et al., 2002; Blankertz et al., 2006). This is the most used approach.

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[1] In this article, we do not consider BCI based on Event Related Potentials, such as P300-based BCI. Indeed, these latter rely on brain responses evoked by external stimulus and as such they involve practically no human training (Wolpaw et al., 2002; Fazel-Rezai et al., 2012).

[2] Neurofeedback consists in providing the user with a real-time feedback about his/her own brain activity so that he/she can learn to voluntarily control it.

These two approaches differ in the way the decoder works (fixed vs optimized on EEG data) and on the instructions provided to the user (e.g., moving the cursor by modulating brain activity in a way to be identified vs performing a given mental task), but the remaining elements of the training approaches are roughly similar. First, the global objective is the same, typically moving an element on screen in different directions depending on the EEG pattern produced. The ways feedback is provided are similar since it is generally a uni-modal (generally visual) feedback indicating the mental task recognized by the decoder together with the confidence in this recognition. It is generally represented by an extending bar or a moving cursor (Neuper and Pfurtscheller, 2010) (see, e.g., **Figure 2**). Typically, the bar/cursor extends in the required direction if the mental task is correctly recognized and extends in the opposite direction otherwise. The speed of the bar extension or of the cursor movement is also proportional to the decoder confidence in its decision. Finally, the training protocols are also similar. Indeed, with both approaches, the user is trained following a synchronous (or system-paced) protocol, i.e., a protocol in which the user is required to do specific tasks (e.g., extending the bar toward the left by imagining left hand movements) in specific time periods only. The same protocol is usually repeated until the user has learnt the BCI skill, i.e., until he/she has achieved a given performance, usually in terms of rate of correct mental state recognition.

2.2. RESEARCH ON ALTERNATIVE HUMAN TRAINING PROTOCOLS FOR BCI

As we will see later, the training approaches described above have many limitations according to instruction design principles, but are the protocols classically used in current BCI designs. Fortunately, some research groups have explored alternative methods, more in line with instructional design guidelines. We review them below.

Most research on BCI human training approaches so far have focused on studying the impact of various kinds of feedback. In particular, fundamental research on feedback was conducted in the early days of BCI research. Indeed, McFarland et al. showed that feedback was necessary for initial learning of the BCI skill (McFarland et al., 1998). However, they showed that once the BCI skill is learned, then feedback may not be necessary anymore, at least in the short-term and for BCI based on sensori-motor rhythms. They also showed that continuous feedback can have either facilitory or inhibitory effects depending on the learner. The study of Neuper et al. suggested that continuous feedback lead to more efficient BCI learning than delayed discrete feedback (Neuper et al., 1999). In Neuper et al. (2003), they also explored a free training session, in which the BCI user could explore the mental imagery task as he liked, without instructions from the computer. This free training session seemed to have a positive learning impact on the user's EEG patterns (with changes in Event Related Synchronisation/Desynchronisation in the expected direction), although no formal comparison with a training protocol without such session was performed. Kübler et al. used both a continuous feedback during cursor movement and a discrete delayed feedback at the end of each trial, which prove successful to teach BCI users to control their Slow Cortical Potentials (SCP) (Kübler et al., 1999). It is worth mentioning that the discrete delayed feedback was an emotionally charged one, more precisely a smiley face. How an emotionally charged feedback compare to an emotionally neutral one was not formally explored though. Interestingly enough, Kübler et al. also found that, with this kind of training protocol, the performance obtained during early training sessions could predict the number of sessions needed to achieve BCI control (Kübler et al., 2004).

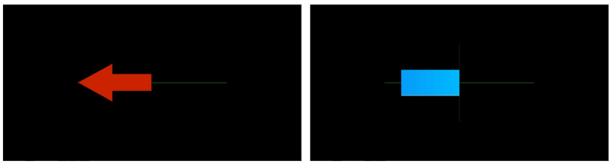

FIGURE 2 | Example of the display of a classic BCI training protocol. Left: An arrow pointing left indicates the learner to imagine a left hand movement. **Right**: A feedback bar is provided to the learner. The direction and length of this bar indicate the classifier output and thus the recognized mental task. Indeed, the bar extends toward the left for an identified imagined left hand movement, and toward the right for an identified imagined right hand movement.

Some authors explored richer and multidimensional feedback, in order to provide BCI users with more information about their brain activity. For instance (Arrouët et al., 2005; Hwang et al., 2009) used as feedback 2D or 3D topography of cortical activation obtained by inverse solutions. Interestingly enough, Hwang et al. have shown that a neurofeedback session in which the user was shown a real-time cortical map of his/her brain activity increased motor imagery-based BCI performances (Hwang et al., 2009). Still exploring multidimensional feedback, Kauffman et al. provided their BCI users with a cursor indicating not only the integrated classifier output, but also its instantaneous sign and absolute value, coded as the color and intensity of this cursor (Kaufmann et al., 2011). Results suggested that users can deal with a multi-dimensional feedback without decrease in performance, although neither without significant increase in performance here. Using BCI with game-like, 3D or Virtual Reality (VR) feedback environments have also been shown to increase BCI performances (Leeb et al., 2006; Lécuyer et al., 2008; Nijholt et al., 2009; Ron-Angevin and Diaz-Estrella, 2009; Lotte et al., 2013). In the same vein, feedback from multiple users playing a BCI-based game together has been shown to increase BCI performances as compared to feedback provided from the user only, during a single-player version of the same game (Bonnet et al., 2013).

Some groups also explored alternative modalities for the feedback, such as tactile feedback (Cincotti et al., 2007) or auditory feedback (Nijboer et al., 2008). Both studies obtained BCI performance similar to that obtained with visual feedback. Some groups also explored multimodal feedback, which combined two modalities. These studies have provided mixed results: a combination of audio and visual feedback has been shown to decrease BCI performances (Hinterberger et al., 2004) while a combination of haptic (a.k.a, proprioceptive) and visual feedback increased performances (Gomez Rodriguez et al., 2011; Ramos-Murguialday et al., 2012).

Some studies showed that biased feedback (i.e., making the user believe he/she did better than what he/she actually did) or positive feedback (i.e., only providing feedback when the task was performed correctly) can improve performances, at least for new or inexperienced BCI users (Kübler et al., 2001; Barbero-Jimenez and Grosse-Wentrup, 2010; Faller et al., 2012). Positive feedback was shown to decrease performance for advanced BCI users though (Barbero-Jimenez and Grosse-Wentrup, 2010), as well as after too many sessions with only positive feedback (Kübler et al., 2001). Vidaurre et al. provided the user with a feedback that was initially generic and progressively more and more specifically tuned for this user (Vidaurre et al., 2011). Indeed, they use a classifier that was initially subject-independent, using a generic set of channels, and progressively adapted the classifier and the channels used to the BCI user. This progressive classifier (and thus feedback) adaptation enabled BCI users initially suffering from the BCI inefficiency to control the BCI.

Aside from work on feedback for BCI, there have been a couple of studies on other components of the BCI training protocol, namely on instructions and training tasks. The work of Neuper showed that specifically instructing the user to perform kinesthetic imagination of movements rather than visual imagination of movements substantially improved performances (Neuper et al., 2005). Concerning training tasks, McFarland et al. successfully used progressive training tasks by first training users to performed 1D control of a cursor, then 2D control and finally 3D control (McFarland et al., 2010).

It should be mentioned that although the training procedure and the signal processing algorithms used are important factors in BCI efficiency, these are not the only ones. In particular, recent works have shown that individual users' characteristics, such as psychosocial and physiological parameters (e.g., gender, instrument playing, fine motor skills) or brain structures, can predict control performances for Mu-rhythm based BCI (Blankertz et al., 2010; Halder et al., 2011, 2013; Hammer et al., 2012; Randolph, 2012).

In summary, although there have been many more research efforts on signal processing and machine learning for BCI, there still have been some interesting research works on training procedures for BCI. As we will see later, several of these work actually comply with guidelines from instructional design literature. Unfortunately, the results from these study are generally not used nor considered in current BCI training protocols. Actually, the BCI training protocols currently used are still the classical ones described in section 2.1, who suffer from many limitations. Indeed they satistify very few of the instructional design guidelines provided by the educational research community, as the next section exposes.

3. FLAWS IN BCI TRAINING PROTOCOLS

Current BCI training approaches, as described in section 2.1, have made BCI control possible, which was a great step forward. Nevertheless, while they made BCI control possible, BCI control still has a poor performance, in terms of speed or accuracy, and many people cannot use a BCI at all (Allison and Neuper, 2010), at least using current training approaches. However, research results in the field of instructional design, educational psychology and human factors have identified the key elements for efficient training across a number of different skills, e.g., language, mathematical, memory or motor skills, making them generic and relatively skill-independent. Even though BCI training approaches are instructional designs (they aim at teaching the BCI skill), most of them unfortunately do not follow guidelines provided by these research fields. As we will see below, they are actually quite far from an ideal instructional design, which may explain the still poor performances of BCI and the high rate of illiteracy/inefficiency. In the following, we analyze the design of BCI training approaches at three levels: (1) at the level of the feedback, (2) at the level of the instructions provided to the user and (3) at the level of the training tasks. For each level, we identify the flaws in BCI approaches according to instructional design literature and propose new directions that are likely to make the designs more efficient.

3.1. FEEDBACK

Feedback is known to be a significant factor to motivate learning (Shute, 2008). Moreover, it has been shown that providing extensive feedback to a user leads to efficient and high quality learning (Hattie and Timperley, 2007). However, this is not true for any kind of feedback, and a poorly designed feedback could actually deteriorate motivations and impede a successful learning (Shute, 2008).

What should a good feedback be like then? To be effective, "feedback should be non-evaluative, supportive, timely and specific" (Shute, 2008). It should indicate the user how to improve the task (Shute, 2008) rather than just indicating whether the task was done correctly or not (Hattie and Timperley, 2007; Moreno and Mayer, 2007; Shute, 2008). It should signal a gap between current level of performance and some desired level of performance, hence reducing uncertainty for the user about how he is doing (Hattie and Timperley, 2007; Shute, 2008). In other words, Hattie describes a good feedback as a feedback that can answer the following questions: "where am I going? (what are the goals), how am I going? (progress toward the goal), where to next? (what activities need to be undertaken)" (Hattie and Timperley, 2007). Feedback should also lead to a feeling of competence, in order to increase motivation (whether intrinsic or extrinsic) and thus learning efficiency and efforts (Ryan and Deci, 2000). Finally, an ideal "feedback needs to be clear, purposeful, meaningful" (Hattie and Timperley, 2007).

In contrast, classical BCI feedback satisfies few of such requirements. Indeed, BCI feedback is evaluative and corrective, i.e., it only indicates the user whether he/she performed the task correctly. Also, being only corrective, it does not aim at supporting the user. BCI feedback also does little to help the user feel competent at BCI control. More importantly, BCI is non-specific since it does not explain why or what was good or bad about the task performed by the user. With the machine learning approach, BCI feedback might also be unclear and meaningless, if it is based on a classifier trained on incorrectly performed mental tasks. Unfortunately, this situation is likely, since first time users have by definition never used a BCI before, and thus cannot be expected to perform the required mental tasks perfectly from the start. In other words, for new BCI users who cannot do the mental task correctly from the start, the feedback will indicate them they have done well if they performed the mental task as badly as they did the very first time, during the calibration data collection. It would therefore reinforce bad mental task performance, which is unlikely to be meaningful. Finally, BCI feedback provided during training is often very simple and crude, while during actual BCI operation, to control an actual application, the environment and feedback is often rich and complex. This complexity and environment mismatch may be another source of difficulty for the user.

To work and to be efficient, BCI feedback should therefore be (1) non-evaluative and supportive, (2) meaningful and (3) specific, i.e., explanatory. Additionally, BCI feedback could also benefit from multimodality and more engaging environments.

The need to be non-evaluative and supportive seems to encourage the use of positive feedback, i.e., feedback only provided when the user did well, to let him/her know he/she did well. Hattie indeed recommends the use of positive feedback, at least for beginners and people who want to do the task (as opposed to people who have to do it) (Hattie and Timperley, 2007). For highly self-efficacious learners, Hattie and Timperley (2007) advocates the use of disconfirmatory feedback (a.k.a. negative feedback—i.e., noting when the task was not done properly). The few BCI studies that explored biased or positive feedback obtained results in line with such suggestions. Indeed, they showed that positive feedback was beneficial for new or inexperienced BCI users, but harmful for advanced BCI users (Kübler et al., 2001; Barbero-Jimenez and Grosse-Wentrup, 2010; Faller et al., 2012).

The need to provide meaningful feedback suggests that, in the machine learning approach to BCI, the classifier used should be carefully selected. In particular, if the user initially obtains bad performances, it may be worth not using a classifier trained on the data from this user (which are examples of badly performed mental tasks and thus would lead to feedback reinforcing a wrong strategy). Rather, it could be worth using, at least initially, a subject-independent classifier (Fazli et al., 2009; Lotte et al., 2009), trained on data corresponding to mental tasks correctly performed by other users. In this way, the classifier output is more likely to be a meaningful feedback, indicating (at least roughly) when the user did the mental task correctly. The work on co-adaptive training by Vidaurre et al. is an example of such an approach, with the training protocol starting with generic and subject-independent features and classifier, progressively adapted to the user during training (Vidaurre et al., 2011). It is unclear though whether a subject-independent classifier could be designed for patients, who may have larger inter-subject variability.

More importantly, BCI feedback would theoretically benefit from being specific and explanatory. This means that ideally, the feedback should indicate the user what he/she did well or wrong, and how to improve this. For the moment, BCI feedback is only corrective, which means the user has to figure out what he/she did not do well all by him/herself, without any explanation from the feedback. Since one cannot be easily aware of his own brain activity without neurofeedback, this is likely to be very difficult or even impossible for some users. BCI feedback could therefore provide more information about the brain activity features used by the BCI rather than simply the classifier output (which aggregates everything together). We provide below a couple of suggestions to try to do so:

- Providing as feedback the value of a few relevant features. This would indeed provide a richer feedback, hopefully giving more clues to the user as to what may be going well or not. The number of features shown as feedback should be kept small however. Indeed, an efficient feedback should not be too long nor too complex, and should be provided in manageable pieces (Shute, 2008). Moreover, human working memory being limited to seven information elements at a time on average, one should show less than seven features as feedback (Sweller et al., 1998). Similarly, one could provide the user with a global picture of his/her brain activity, e.g., a 2D or 3D topography of cortical activation obtained by inverse solutions. This has been proved efficient in the study of Hwang et al. (2009).
- Showing users a feedback describing the actual quality of the mental task he/she performed. So far, the quality of the mental tasks has been mostly assessed using classification-based measures, e.g., the distance to the separating hyperplane with linear classifiers. However, this may not be easy to understand for the user. Alternatively, we could identify the properties of a good mental task (e.g., of a good imagined movement), e.g., in terms of strength of the Event Related Desynchronisation/Synchronisation (ERD/ERS) (Pfurtscheller and Neuper, 2001), localization, spatial spread and specificity, stability over time of this ERD/ERS (on this topic, see e.g., Friedrich et al., 2013), etc. Then we would use as feedback a measure of these properties for the task performed by the user. Alternatively, we could also feedback the difference between these properties measures for the current mental task and their value for an optimal mental task. Indeed, such a feedback would actually indicate a gap between current performances (the mental task performed by the user) and a desired level of performance (a good mental task) (Hattie and Timperley, 2007; Shute, 2008). This would also enable to focus on the user's progress, which is recommended (Hattie and Timperley, 2007; Shute, 2008), and thus help him/her to feel competent (Ryan and Deci, 2000).

Current BCI feedback, being mostly visual and unimodal, may also benefit from multimodality. Although research on the benefits of providing learners with multiple representations has produced mixed results, a carefully designed multimodal feedback may prove useful (Ainsworth, 2006; Merrill, 2007). As mentioned in section 2.2, research on multimodal feedback for BCI has also produced mixed results. These mixed results are well summarized by Ainsworth, who mentioned that "By switching between representations learners can compensate for weaknesses in their strategy. However, if learners are attempting to relate different representations, then this may provide a source of difficulty" (Ainsworth, 2006). This work also suggests that the content of the representations may be more important than the modalities used for each representation (Ainsworth, 2006). In particular, an efficient multimodal representation should use the same formats and operators on each representation, i.e., one should be able to interpret the different representations in a similar way, using the same kind of mental analysis (Ainsworth, 2006). The different representations should also have a similar specificity, i.e., the same granularity of explanatory content (Ainsworth, 2006). Finally, there should be some redundancy between representations so that the user can easily relate them (Ainsworth, 2006). This suggests that a multimodal BCI feedback respecting these guidelines might be useful. For instance, the work in Hinterberger et al. (2004) used different granularity for the auditory and visual modalities, the visual feedback being continuous while the audio one was discrete. This might explain why it decreased BCI performances. On the contrary, the works in Gomez Rodriguez et al. (2011) and Ramos-Murguialday et al. (2012) used the same granularity for both visual and haptic feedbacks, which increased BCI performances.

It should also be mentioned that high quality learning also requires authentic motivation (Ryan and Deci, 2000). This means the feedback and the feedback environment should be inherently motivating and relevant for the learner and have an appeal of novelty, challenge, real-world relevance or aesthetic value (Ryan and Deci, 2000; Merrill, 2007). This supports the use of more engaging feedback environments rather than boring and basic feedbacks such as a classic bar or cursor feedback. Results observing that using BCI with game-like, 3D (even in non-immersive settings) or Virtual Reality (VR) feedback environments increase performances are thus in line with these recommendations (Lécuyer et al., 2008; Lotte et al., 2013). This may also be expected to help the user getting used to richer and more complex environments, thus lowering the mismatch between the feedback provided during training and during real-world use.

3.2. INSTRUCTIONS

According to instructional design, BCI training approaches could also be improved at the level of the instructions provided to the user before actually starting the training. Indeed, in current BCI training procedures, instructions are rarely considered, and often not mentioned in the papers. Most of the time they consist in asking the subject to perform the targeted mental tasks, or to move the cursor or bar in the required direction. An important exception is the work of Neuper et al. on the necessity to instruct users to perform kinesthetic rather than visual motor imagery (Neuper et al., 2005). This suggests that instructions are important, which is confirmed by instructional design literature (Hattie and Timperley, 2007; Shute, 2008). Indeed, it is known that feedback is more effective when goals are clearly defined and specific (Hattie and Timperley, 2007; Shute, 2008). This stresses that when providing instructions about the BCI training procedure to a user, we should also clearly state the goals and objectives of the training. The objective of a BCI training session may not really be to move a bar left or right nor to imagine movements. Rather, it should be to help the user in producing clear, specific and stable brain patterns. This goal could therefore be explicitly mentioned to the user so that he/she knows the targeted direction and thus what is expected from him/her. In this way he/she would benefit more from the feedback to reach this goal.

Instructional design literature also stresses the need for pretraining or at least initial knowledge or experience on which the training can be based and built (Hattie and Timperley, 2007; Merrill, 2007; Moreno and Mayer, 2007). In the same vein, it is also recommended to demonstrate the knowledge or skill to the student before he actually learns to master it (Merrill, 2007). Both this initial experience and demonstration are usually missing in BCI training protocols. This suggests that BCI training might be made more efficient by, e.g., before the actual BCI practice, instructing the subjects to remember a situation in which they may have used the task they will mentally imagine to drive the BCI. For instance, in the case of motor imagery-based BCI, at the beginning of a session subjects could be instructed to vividly remember a situation in which they performed a given movement (e.g., during a sport session) before imagining it during the subsequent BCI use. This would activate their prior experience with the task they will imagine, which is expected to make the learning easier (Merrill, 2007). Interestingly enough, Halder et al. showed that the ability to recall sensorimotor programs was indeed correlated to BCI performances (Halder et al., 2011). Similarly, showing the BCI learner a demonstration of a successful BCI use, together with a demonstration of BCI feedback during correctly performed mental tasks (see section 3.1), might also promote the learning of the BCI skill (Merrill, 2007).

Feedback itself is also an element on which instructions could be provided. Indeed, for the feedback to be efficient, the learner should understand the representations involved (Ainsworth, 2006). For the learner, this can involve learning to ignore potentially erroneous intuitions that he/she may have about the meaning of the feedback. Some researchers even argue that learners should be taught how to interpret and understand the representations and thus the feedback (Ainsworth, 2006). This suggests that instructions should also be provided to the BCI users in order to explain them the meaning of the feedback. This seems particularly important if the feedback is related to a classifier output, whose actual meaning (e.g., the distance to a separating hyperplane) is unlikely to be intuitive for people not familiar with classification, i.e., for most real-life BCI users.

3.3. TASKS

The last part of BCI instructional design that could be improved is related to the tasks users have to complete. As mentioned before, BCI training tasks are mostly synchronous (a.k.a., system paced) and repeated identically until the users has learned the BCI skill. However, research on education and learning recommends to follow a different approach (Sweller et al., 1998; Ryan and Deci, 2000; Ainsworth, 2006; Hattie and Timperley, 2007; Shute, 2008).

In their book "The media equation," Reeves and Nass (1996) showed that we respond similarly to mediated reality and to real world equivalents: As boring and repetitive teachers are seldom inspiring the engagement and attention necessary for an optimal learning experience, boring and repetitive learning programs have the same effect. Accordingly, to increase the efficiency of computer mediated learning, and specifically of BCI-control learning, the user needs to be presented with an involving and engaging learning environment.

Accordingly, Nijboer et al. (2008) have shown that mood and motivational factors, such as mastery confidence and incompetence fear, are relevant for learning to control a SensoriMotor Rhythm (SMR) BCI. In a longitudinal patient study, Nijboer et al. (2010) found that an increase of SMR-BCI performance correlates with the motivational factor of challenge. Similarly, Kleih et al. (2011) found that motivational factors of challenge and incompetence fear correlate positively with SMR-BCI performance. During learning tasks, different types of motivation can increase the engagement and efficiency of the user (Ryan and Deci, 2000). The strongest motivation, intrinsic motivation, is anchored in the individuals most basic urges: the feeling of competence, autonomy, and relatedness. By appealing to these basic needs in the task construction for BCI, the user's motivation and task engagement can be increased.

To increase the feeling of competence, in general, training tasks should be progressive and adaptive: the learners should first manipulate the least complex representations and should then be progressively introduced to new representation as his/her expertise grows (Ainsworth, 2006; Merrill, 2007). In a similar fashion, the training protocol should provide the user with assignments that are challenging (Hattie and Timperley, 2007), but still achievable (Shute, 2008). Finally, studies have revealed that students could increase their efforts if these can lead to more challenging tasks or higher quality experiences (Hattie and Timperley, 2007). This supports that BCI training protocols and tasks could benefit from being adaptive, with a difficulty that increases as the user increases his/her skills with BCI. For instance, the user could be asked to try out a single mental task at the beginning, rather than all of them at once. Then, he/she will be asked to perform different mental tasks as he/she starts to master the initial ones. The adaptive training protocol of McFarland et al. (1D-control, then 2D, then 3D) made 3D cursor control possible with EEG-based BCI for the first time (McFarland et al., 2010), which seems to support the need for progressive training tasks. Moreover, it has been shown that scaffolding also enhances learning in early stage of training, but should be removed in later stages (Shute, 2008). For instance, in cases where a motor imagery-based BCI is used by individuals with residual motor capabilities or by non-handicapped users, real movements can be used as a scaffold for motor imagery (Higashi et al., 2011). It is an easy-to-manage starting point for training, which then can be slowly replaced by quasi-movements using an EMG-biofeedback approach (Nikulin et al., 2008). Such a gradual transfer from well-known or simple tasks to new tasks initially minimizes the cognitive demand on the users during training, and hence the risk to frustrate and demotivate them.

Regarding the feeling of autonomy, several authors stressed that offering learners the possibility to proceed at their own pace increases their motivation and makes them learn more efficiently (Ryan and Deci, 2000; Moreno and Mayer, 2007; Shute, 2008). This suggests that BCI training protocols could include more free or even self-paced BCI sessions. In other words, users could benefit from being offered—at least from time to time—the possibility to decide the mental task they will perform, rather than always doing the one instructed by the program. They could be offered to do so either when instructed by the computer (i.e., using a so-called synchronous BCI) or, which should be even better, whenever they want too (i.e., using a so-called asynchronous/self-paced BCI). Moreover, self-paced BCI sessions would give time to the users to reflect upon the mental task they did and the corresponding feedback received, which is also recommended for efficient learning (Moreno and Mayer, 2007). Neuper et al. explored such a free self-paced session with a single patient and obtained positive results (Neuper et al., 2003). Although no formal comparison with classical approaches were performed in this study, this would still suggest that including self-paced sessions may prove useful for BCI training.

Related to the mood and motivation of the user is the creation of an emotionally appealing task environments during the learning process. Um et al. (2012) showed that these can facilitate learning by the creation of positive emotions. Theoretically, the impact of emotions on learning can be divided into quantitative effects, e.g., on long-term memory retention, and qualitative effects, e.g., on cognitive organization and creativity. For BCI task acquisition, the retention of the performed mental task and a flexibility during the learning process, e.g., trying different variations of the mental tasks at hand, might be relevant factors that lead to increased performance of the subject. Additionally, excitement and interest created by appealing task environments, such as computer games can also increase the level of activation and engagement of the user (Plass-Oude Bos et al., 2010). However, it is not necessarily the case that negative emotions have a negative impact on learning. Kort et al. (2001) mention that negative emotions or cognitive-emotive states can be useful and integral parts of the learning process. For example, they can lead to an activation of the learner, and initiate changes in an unsuccessful approach or the "unlearning" of false and impeding beliefs. On the other hand, there is also evidence for the detrimental effects additional emotional information can have on the learning process. The reason for these negative effects of emotion during learning is assumed to lie in the additional load on working memory that emotional information can pose and on the interference with the main learning task. Care should therefore be taken when adding emotion-inducing elements to the learning task (Um et al., 2012).

Furthermore, educational research has shown that variability over training tasks and problems encourages the learners to build abstractions since it increases the probability to identify useful features and strategies and to distinguish them from irrelevant ones (Sweller et al., 1998; Ainsworth, 2006). This suggests that BCI training tasks could also include variety in the tasks the users have to complete. Rather than doing exactly the same tasks over and over again, e.g., imagining the same left and right hand movements, the users could be asked to perform slightly different tasks from one trial to the next. For instance, the user would still be asked to perform imagined movements, but he/she could be asked to vary the speed of the imagined movement, its strength, the duration of the imagination, the gesture imagined, etc. This may help the user identifies successful mental strategies as well as the important characteristics of a good mental task.

Finally, it is also known that every student is different and thus that ideally, different training procedures should be used

Table 1 | Summary of desirable properties of a good instructional design with corresponding suggestions to improve human training protocols for BCI.

Level	Properties of a good instructional design	Corresponding suggestions for BCI training protocols
Feedback	- Non-evaluative and supportive feedback (Hattie and Timperley, 2007; Shute, 2008) - Feedback that conducts to a feeling of competence (Ryan and Deci, 2000)	Provide positive feedback (feedback only indicating when the user did right) only for beginners, and disconfirmatory feedback for advanced users
	- Clear and meaningful feedback (Hattie and Timperley, 2007)	Start with a subject-independent classifier for users with poor initial performances
	- Explanatory and specific feedback (Hattie and Timperley, 2007; Shute, 2008) (Moreno and Mayer, 2007) - Feedback that signals a gap between current and desired performances (Hattie and Timperley, 2007; Shute, 2008)	Provide more information about what was right or wrong about the EEG patterns produced by the user: - Provide as feedback the value of a few (less than seven) relevant EEG features - Provide as feedback some measure of quality of the mental imagery
	- Multimodal feedback (Ainsworth, 2006) (Merrill, 2007)	Provide a multimodal feedback (e.g., visual + haptic), with the same granularity and specificity for each modality, with some redundancy between them
	- Engaging feedback and environment (Ryan and Deci, 2000)	Represent the feedback as an interaction with a game element (e.g., a 3D car)
Instructions	- Goals should be clearly defined (Hattie and Timperley, 2007; Shute, 2008)	Expose the real goal of BCI training, i.e., to produce clear, specific and stable EEG patterns
	- The meaning of the feedback should be explained (Ainsworth, 2006)	Explain what the BCI feedback means, particularly for non-intuitive feedback such as the classifier output.
	- Prior knowledge should be activated (Merrill, 2007; Moreno and Mayer, 2007) - The skill to be learned should be demonstrated (Merrill, 2007)	- Instruct the users to remember situations in which they used the task they will imagine - Demonstrate successful BCI use and BCI feedback during correct task performance
Tasks	- Progressive and adaptative tasks (Ainsworth, 2006; Merrill, 2007) - Tasks that are challenging but still achievable (Hattie and Timperley, 2007; Shute, 2008)	Use adaptive BCI training protocols with increasing difficulty (e.g., progressively increasing the number of mental tasks to be mastered)
	- Need for autonomy and work at the user's own pace (Ryan and Deci, 2000; Shute, 2008) (Moreno and Mayer, 2007)	Include more training sessions with free and/or self-paced BCI use
	- Motivation and positive emotions promote learning (Ryan and Deci, 2000; Um et al., 2012)	Using positive emotion-inducing training tasks e.g., including gaming mechanisms
	- Need for variability over tasks and problems (Sweller et al., 1998; Ainsworth, 2006)	Include variety in the mental tasks to be performed, e.g., change in speed or duration of the mental imagery
	- Adapt the training procedure to the student (Hattie and Timperley, 2007; Shute, 2008)	Matching BCI training protocols to users' characteristics

It should be noted that such suggestions are only based on theory, and will need to be formally validated.

for different people (Hattie and Timperley, 2007; Merrill, 2007; Shute, 2008). As such, among the different variations of training protocols mentioned, it could be necessary to identify—through experiments—those that are the most appropriate for which kinds of users' characteristics. These characteristics describe important features of the learner, either cognitive, psychological or physiological, that might influence the way they use and learn BCI, such as age, gender, education level, video game experience, spatial abilities, etc. [see, e.g., Larrue et al. (2012) where users' characteristics where controlled in a study comparing navigation in VR with a BCI and with a treadmill]. A few studies have found correlations between psychological parameters and SMR-BCI control performances (Hammer et al., 2012; Randolph, 2012), which would suggest that matching users' characteristics to the corresponding BCI type is likely to optimize control performances. Similarly, matching training protocols to users' characteristics may make BCI training more efficient.

On a more prospective side, it has been observed that people regularly exposed to video games had improved visual and spatial attention, memory and mental rotation abilities (Green and Bavelier, 2003; Feng et al., 2007; Boot et al., 2008). Extensive video-game practice has also been shown to improve the efficiency of movement control brain networks and visuomotor skills (Granek et al., 2010). Since these various skills are involved in some mental tasks used to drive BCI [e.g., mental rotation of geometric figures, motor imagery, remembering familiar faces, . . . (Lotte, 2012; Friedrich et al., 2013)], this suggests that BCI users might improve their mastery of BCI by performing training tasks that do not involve the BCI system, such as by playing various video games. To the best of our knowledge, correlation between regular video game practice and BCI performance has not been shown yet for BCI based on mental tasks, but has been observed for BCI based on Steady-State Visual Evoked Potentials (SSVEP) (Allison et al., 2008). This suggests that having BCI users practicing (non-BCI-based) video games might be a promising training task to improve their BCI control skills.

4. CONCLUSION

Based on a study of educational psychology and instructional design research papers, we have highlighted that BCI training approaches were very likely to be inappropriate and may benefit from multiple improvements that could increase BCI performances and reduce BCI illiteracy/inefficiency. We have identified the flaws of BCI training protocols from the perspective of instructional design and proposed some suggestions that are theoretically expected to address these flaws and make BCI training more efficient. Naturally, these suggestions are only based on instructional design principles and would need to be formally explored and validated to assess their actual efficiency. The properties of a good training protocol and the corresponding suggestions for BCI training are summarized in **Table 1**. Overall, we suggest to provide a BCI feedback that is (1) positive feedback in early training stage and disconfirmatory in later stages, (2) meaningful, i.e., not related to the output of a classifier trained on incorrectly performed mental tasks, and (3) specific and explanatory, i.e., which provides the user more information about his/her brain activity than the classifier output. Instructions may be improved as well, by defining a clear and specific learning objective and explaining it to this user. Instructions may also be provided to explain the feedback meaning, to instruct the subject to activate prior experience with the task he/she will use, and to demonstrate correct BCI use. Finally, BCI training tasks may also be improved by (1) being adaptive with increasing complexity and difficulty, (2) including self-paced sessions, (3) being more engaging and (positive) emotion-inducing, (4) including a variety of tasks, and (5) matching users' characteristics. We also showed that the few papers that studied BCI training procedures are generally in line with these recommendations derived from instructional design literature. This further stresses the relevance of working on BCI instructional design. In turn, this also suggests that training protocols for BCI studies and designs should deserve more attention. As such, we would recommend BCI authors to carefully describe the training protocols they use in their papers, so that the whole BCI design could be fairly understood and assessed. Similarly, BCI training protocols, as many BCI components, would benefit from standards, so as to enable fair comparisons between BCI designs.

With this literature study, we hope to provide a new perspective on the well-known performance issue of BCI. We also hope that this will bring the BCI community attention to a mostly neglected aspect: much still needs to be explored about training procedures for BCI, which also means that BCI performances still have much potential for further improvement. We provide here a number of suggestions for further research, which we expect will contribute to motivate researchers to explore these areas and to further advance the field of BCI design.

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Learning to modulate one's own brain activity: the effect of spontaneous mental strategies

Silvia E. Kober*[1], *Matthias Witte*[1], *Manuel Ninaus*[1], *Christa Neuper*[1,2] and *Guilherme Wood*[1]*

[1] *Department of Psychology, University of Graz, Graz, Austria*
[2] *Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, Graz, Austria*

Edited by:
Reinhold Scherer, Graz University of Technology, Austria

Reviewed by:
Juliana Yordanova, Bulgarian Academy of Sciences, Bulgaria
Robert Leeb, Ecole Polytechnique Fédérale de Lausanne, Switzerland
Vincenzo Romei, University of Essex, UK

****Correspondence:***
Guilherme Wood, Department of Psychology, University of Graz, Universitaetsplatz 2/III, 8010 Graz, Austria
e-mail: guilherme.wood@uni-graz.at

Using neurofeedback (NF), individuals can learn to modulate their own brain activity, in most cases electroencephalographic (EEG) rhythms. Although a large body of literature reports positive effects of NF training on behavior and cognitive functions, there are hardly any reports on how participants can successfully learn to gain control over their own brain activity. About one third of people fail to gain significant control over their brain signals even after repeated training sessions. The reasons for this failure are still largely unknown. In this context, we investigated the effects of spontaneous mental strategies on NF performance. Twenty healthy participants performed either a SMR (sensorimotor rhythm, 12–15 Hz) based or a Gamma (40–43 Hz) based NF training over ten sessions. After the first and the last training session, they were asked to write down which mental strategy they have used for self-regulating their EEG. After the first session, all participants reported the use of various types of mental strategies such as visual strategies, concentration, or relaxation. After the last NF training session, four participants of the SMR group reported to employ no specific strategy. These four participants showed linear improvements in NF performance over the ten training sessions. In contrast, participants still reporting the use of specific mental strategies in the last NF session showed no changes in SMR based NF performance over the ten sessions. This effect could not be observed in the Gamma group. The Gamma group showed no prominent changes in Gamma power over the NF training sessions, regardless of the mental strategies used. These results indicate that successful SMR based NF performance is associated with implicit learning mechanisms. Participants stating vivid reports on strategies to control their SMR probably overload cognitive resources, which might be counterproductive in terms of increasing SMR power.

Keywords: neurofeedback, mental strategies, sensorimotor rhythm, gamma, EEG, implicit learning

INTRODUCTION

Using neurofeedback (NF), individuals can learn to modulate their own brain activity. In NF, healthy, age appropriate brainwave activity is rewarded with visual, auditory or even tactile stimulation. In contrast, undesirable patterns of activity are ignored or punished (Coben and Evans, 2010). When participants become successful in regulating their own brain activity, e.g., voluntarily increase specific EEG frequency bands, improvements in cognition and behavior usually follow (Kotchoubey et al., 1999; Wolpaw et al., 2002; Gruzelier and Egner, 2005; Kübler et al., 2005; Kübler and Kotchoubey, 2007; Kropotov, 2009; Coben and Evans, 2010). Hence, there is strong evidence for positive effects of NF training on behavior and cognitive functions. However, researchers have different opinions about underlying mechanisms and processes leading to successful NF performance. There are hardly any reports on how participants can successfully learn to gain control over their own brain activity. In the present study, we addressed this question by focusing on the effects of different mental strategies on NF performance.

Brain signals can be used as a control signal for a brain computer interface (BCI) or to provide NF to participants (LaConte, 2011). Although NF and BCI applications are effective in the rehabilitation and therapy of many disorders, a substantial proportion of participants fail to gain significant control over their brain signals even after repeated training sessions. About 15–30% of potential BCI or NF users cannot attain control over their own EEG (Allison and Neuper, 2010; Blankertz et al., 2010). In the BCI community, the inability to use BCI applications is called "BCI-illiteracy phenomenon" (Blankertz et al., 2010). There are different attempts to explain this phenomenon. In some users of NF or BCI feedback applications, neuronal systems needed for voluntary control might not produce electrical activity detectable on the scalp. Although the necessary neuronal populations are presumably healthy and active in these participants, the activity they produce may not be detectable by a particular neuroimaging method, such as EEG. Another reason might be that some participants produce excessive muscle artifact, which might disturb the feedback signal and hamper the learning effect (Allison and Neuper, 2010). To find possible predictors of the BCI-illiteracy phenomenon, the interest in inter-individual differences in BCI or NF performance is rising. In this context, some researchers found neurophysiological predictors of NF or BCI performance (Neumann and Birbaumer, 2003; Kübler et al., 2004; Blankertz et al., 2010; Halder et al., 2013a,b), others found that psychological factors such as "locus of control" (LOC), degree of concentration, mood, mastery confidence, or motivation can predict NF and BCI performance to some extent (Burde and Blankertz, 2006; Nijboer et al., 2008; Kleih et al., 2010; Hammer et al., 2012; Witte et al., 2013). However, the definite reasons why some people fail to gain significant control over their own brain signals are still unknown.

A first step to identify parameters of success to gain control over one's own brain activity is to define how regulation of physiological parameters such as EEG activity might be learned. In this context, Hammer et al. (2012) defined three different models: The first and in the NF literature most frequently mentioned model is operant conditioning. Operant learning declares that the occurrence of a positively reinforced behavior will increase (Skinner, 1945). Consequently, in NF studies correct or desired brain responses are positively reinforced by getting reward points, a smiling face, etc. (Kübler et al., 1999; Leins et al., 2007; Weber et al., 2011). In NF studies, participants can freely choose different mental strategies to control their own brain activity, which results in trial-and-error learning. By means of trial-and-error, participants use diverse strategies and repeat them when positively reinforced (Curran and Stokes, 2003; Hammer et al., 2012). The second model suggests that the feedback-learning of physiological parameters is comparable with motor learning (Lang and Twentyman, 1976). In a biofeedback study by Lang and Twentyman (1976), participants should learn to control their own heart rate. The authors proposed that the ability to control one's own heart rate could be conceptualized as the acquisition of motor learning. According to Lang and Twentyman, the voluntary control over cardiovascular processes requires a well-organized sequence of activities, movements and symbolic information. These should be the same processes necessary to hit for instance a tennis ball correctly. This model might be transferred to self-regulation of other physiological parameters such as EEG parameters as well (Hammer et al., 2012). Kropotov (2009) also compared the learning procedure during NF training with the technique how we learn motor skills such as to drive a bicycle (Kropotov, 2009). The third model of how to regulate one's own brain activity is the dual process theory (Lacroix and Gowen, 1981; Lacroix, 1986). This theory describes learning as an interaction of feed-forward and feed-back processes. The naïve learner searches for an effective strategy. This cognitive process needs a high degree of attentional resources due to trial-and-error learning. The decision for a mental strategy depends on the provided instruction. If the learner already has an effective strategy, it will be maintained and improved. However, if the learner has no effective strategy, the novice has to design a new motor activation-model. If this model turns out to be successful it will be maintained and improved. In a final step, this process becomes automatic. The learned skill is stored in the implicit memory and its retrieval requires no consciousness any more (Strehl, 2013). According to Lacroix and colleagues, the instruction plays a central role in the learning success. In line with this assumption, Neuper et al. (2005) found differences in the EEG patterns during motor imagery depending on the instruction provided to the participants (Neuper et al., 2005). Participants were told to either imagine a hand-movement kinaesthetically (feeling of movement) or visually (seeing the movement in their mind's eye). Only for the kinaesthetic imagery, EEG activity over sensorimotor areas was comparable to that of actual movement (Neuper et al., 2005). In contrast to typical BCI applications, where very specific instructions can be transmitted to participants straightforwardly (Curran and Stokes, 2003; Friedrich et al., 2012, 2013), the exact instruction given by the experimenters to the participants in NF studies are hardly described in detail (Hoedlmoser et al., 2008).

In summary, one of the core features of successful NF performance is the used mental strategy. However, the effects of spontaneous mental strategies on NF performance are scarcely investigated. A study by Nan et al. (2012) is one of the rare examples investigating different mental strategies used to gain control over the own EEG activity in a NF application. In that study, participants were instructed to employ any strategies they like in an individual Alpha NF training, but they should use only one strategy in each trial. After each trial, participants wrote down the strategy they used to control their own EEG and rated how successful this strategy for self-regulating their EEG was. Nan et al. (2012) reported the subjective self-rating scores of efficiency for each strategy. This analysis of self-comments showed that what is an useful strategy varies among individuals and that the most successful strategies when training their individual Alpha rhythm were related to positive thinking such as thoughts about lover, friend and family (Nan et al., 2012). Moreover, Angelakis et al. (2007) reported similar findings when participants learned to increase their individual Peak Alpha Frequency (PAF) or their Alpha power. Particularly, Alpha amplitude was higher when participants reported to have positive thoughts during training and when they reported that they thought of nothing particular, or had a blank mind during NF training (Angelakis et al., 2007).

In the present NF study, participants were instructed to employ any mental strategy they wanted to increase either their own sensorimotor rhythm (SMR, 12–15 Hz) or high-frequency EEG rhythms (Gamma, 40–43 Hz). The SMR generally emerges when one is motionless yet remains attentive (Sterman, 1996, 2000; Serruya and Kahana, 2008). Hence, one could assume that the best mental strategy to increase SMR power is to be mentally focused and physically relaxed. Several NF studies provide evidence that healthy individuals are able to learn how to *increase* their own SMR amplitude (Tansey and Bruner, 1983; Tansey, 1984; Tinius and Tinius, 2000; Vernon et al., 2003; Egner et al., 2004; Schabus et al., 2004; Hoedlmoser et al., 2008; Doppelmayr and Weber, 2011). However, none of these studies analyzed formally the mental strategies employed by the participants to control SMR power. In BCI studies, amplitude *reductions* of the SMR rhythm can be voluntarily controlled by most participants, for instance by using motor imagery strategies such as imaging a hand or foot movement (Kübler et al., 2005; Blankertz et al., 2010). Though, motor imagery leads to decreased SMR amplitude over the motor cortex (Pfurtscheller and Neuper, 1997; Pfurtscheller and Lopes da Silva, 1999). Voluntary increase in SMR power cannot be reached by motor imagery strategies, which is required in most SMR based NF applications (Tansey and Bruner, 1983; Tansey, 1984; Tinius and Tinius, 2000; Vernon et al., 2003; Egner et al., 2004; Schabus et al., 2004; Hoedlmoser et al., 2008).

A second group of participants should learn to voluntarily increase their Gamma (40–43 Hz) power. Studies on meditators showed that Gamma power was intensified during meditation, and that Gamma is apparently associated with feelings of kindness and compassion (Banquet, 1973; Lutz et al., 2004; Rubik, 2011). Some NF studies could show that people are able to alter the power in the Gamma frequency band voluntarily by means of real-time feedback (Bird et al., 1978; Keizer et al., 2010a,b; Rubik, 2011). However, these NF studies do not provide any concrete explanations or descriptions on how people actually managed to increase or decrease Gamma power voluntarily (Keizer et al., 2010a,b). A study by Rubik (2011) is one of the rare examples aiming to explore inner experiences associated with increased production of Gamma brainwaves in an initial NF experience (Rubik, 2011). Increased Gamma power during an initial NF training session was associated with positive emotions of happiness and love, along with reduced stress. On the basis of the NF study by Rubik (2011) and the studies on meditators one could conclude that the best mental strategy to modulate EEG Gamma activity voluntarily might be to produce positive feelings such as happiness, love, kindness, or compassion.

The aim of the present study was to investigate the effects of spontaneous mental strategies on gaining control over SMR or Gamma activity during repeated NF training, respectively. To this end, naïve NF users wrote down their mental strategies after the first and last NF training session. According to the literature, we expect that different mental strategies have different effects on NF performance. For instance, positive thoughts and thinking on nothing particular should lead to an increased NF performance compared to negative thoughts (Angelakis et al., 2007; Rubik, 2011; Nan et al., 2012). Furthermore, we wanted to examine whether the success of different mental strategies is frequency specific, or if diverse mental strategies lead to the same NF training outcome in the SMR and Gamma group. Since there are no prior NF studies linking concrete mental strategies to voluntary control over SMR or Gamma power, it remains unclear whether similar results will be obtained for the SMR and Gamma NF training or not.

MATERIALS AND METHODS

PARTICIPANTS

A total of 20 healthy participants (10 males and 10 females, aged 40–63 years: Mean age = 46.40 years, *SE* = 1.71) took part in this study. All participants were novices for NF- and BCI-experiments. All volunteers gave written informed consent and were paid for their participation (7€per hour). The ethics committee of the University of Graz, Austria approved all aspects of the present study in accordance to the Declaration of Helsinki. Participants were randomly assigned to one of two NF groups: a SMR group (5 males, 5 females, Mean age = 46.80 years, *SE* = 1.99) and a Gamma group (5 males, 5 females, Mean age = 46.00 years, *SE* = 1.26). The SMR group performed a SMR (12–15 Hz) based NF training. Hence, this group was rewarded whenever their SMR power exceeded a predefined threshold. The Gamma group performed a Gamma (40–43 Hz) based NF training. Therefore, this group was rewarded whenever their Gamma power exceeded a predefined threshold. Participants were not informed about the grouping design, nor did they know that there were different conditions.

NEUROFEEDBACK TRAINING

The EEG signal was recorded from Cz channel (according to the international 10–20 EEG placement system), the ground was located at the right mastoid, the reference was placed at the left mastoid. Furthermore, one EOG channel was recorded. Therefore, the positive electrode was placed above and the negative electrode was placed below the left eye. The signals were amplified by a 10-channel system (NeXus-10 MKII, Mind Media BV). The EEG and EOG signals were digitized at 256 Hz and low-pass filtered with 64 Hz.

The NF paradigm was generated by using the software BioTrace+ (Mind Media BV). Ten NF training sessions were carried out within 3 weeks. Each session consisted of seven runs á 3 min each. The first run was a baseline run. In this baseline run participants saw three moving feedback bars on the screen depicting their own EEG activity but were instructed to relax themselves and not to try to control the bars voluntarily. The subsequent six runs were feedback runs, where participants were instructed to voluntarily control the moving bars.

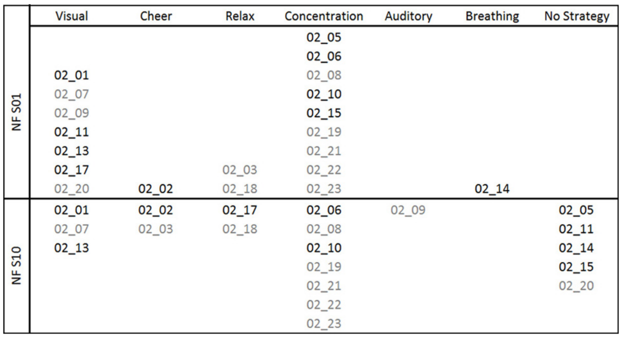
The feedback display contained three moving bars: One big bar in the middle and two smaller bars on the left and right side of the feedback screen. During each three-minute run the feedback bars were continuously moving in a vertical direction. The height of the bar in the middle of the screen reflected absolute SMR (12–15 Hz) band power in real time for the SMR group and absolute Gamma (40–43 Hz) band power in real time for the Gamma group, respectively. The width of the Gamma and SMR band was made identical to prevent possible effects of a bandwidth difference in the Gamma and SMR band (Keizer et al., 2010a,b). Whenever the band power reached an individual predefined threshold in the feedback runs, the color of this bar changed from red to green and participants were rewarded by getting points, which were also displayed at the feedback screen (reward counter). Furthermore, as a reward auditory feedback was provided by means of a midi tone feedback. When the bar was below the threshold it turned red again, the reward counter stopped and no tone was presented. Participants were instructed to try to voluntarily increase this bar. The threshold for the SMR/Gamma bar was adapted after each run. The mean of the SMR/Gamma power of the previous run was taken as SMR/Gamma threshold in the actual feedback run.

In order to prevent augmentation of the SMR or Gamma signal by muscle artifacts, such as movements or eye blinks, two inhibit-bands were used, represented on the screen by the two smaller vertical moving bars on the left and right side of the display. The small bar on the left side of the feedback screen depicted EEG band power between 4 and 7 Hz indicating eye blinks, and the small bar on the right side depicted EEG band power between 21 and 35 Hz indicating movements and other high frequency disturbances (Doppelmayr and Weber, 2011; Weber et al., 2011). Artifact rejection thresholds were set for each participant individually (mean of baseline run + 1 *SD*), suspending feedback when eye-movements or other muscle activity caused gross EEG fluctuations. Hence, participants were instructed to keep these two bars as small as possible, but they were not told that they could influence the height of these bars by muscle activity or eye-movements. Participants were not rewarded when these two controlling bars were above their related thresholds even when SMR/Gamma was above the individually defined threshold.

MENTAL STRATEGY

After the first and the last NF training session, participants were asked which mental strategy they have used to gain control over the moving bars. Before the NF training, we did not prescribe any specific strategies which might be useful to control the bars. Participants were only instructed to be mentally focused and physically relaxed during the NF training in order to avoid producing too many artifacts. Hence, during the NF trainings, participants could utilize any mental strategy they wanted. To help participants finding out the efficient strategy for self-regulating their EEG, they were asked to write down the strategy used and its effect after the first and the last training session.

The reported mental strategies were divided into different categories: Visual strategies, auditory strategies, cheering strategies, relaxation, concentration, breathing, and no strategy. The reported mental strategies and the subsequent categorization process are described in **Table A1** of the Appendix in more detail. Mental strategies, which were classified as visual strategies, contained imagination of colors or objects. Auditory strategies reflected the imagery of tones or sounds. Participants using cheering strategies tried to increase the SMR/Gamma bar by cheering it on. Others tried to relax as much as possible to increase SMR/Gamma. Concentration strategies refer to focused attention and concentration on the moving bars. Breathing methods were used as well, where participants tried to consciously regulate their breath to gain control over their own EEG. And the last category included all reports in which the participants did not name any specific strategy. In **Figure 1**, the frequencies of the mental strategies used during the first and the last NF training session are shown, separately for the SMR (black font color) and Gamma group (gray font color). For instance, three participants of the Gamma group used a visual strategy during the first NF session. One of these three participants still used the visual strategy during the last NF session, one of them switched to an auditory strategy and one reported no specific mental strategy during the last training session any more.



	Visual	Cheer	Relax	Concentration	Auditory	Breathing	No Strategy
NF S01	02_01 02_07 02_09 02_11 02_13 02_17 02_20	02_02	02_03 02_18	02_05 02_06 02_08 02_10 02_15 02_19 02_21 02_22 02_23		02_14	
NF S10	02_01 02_07 02_13	02_02 02_03	02_17 02_18	02_06 02_08 02_10 02_19 02_21 02_22 02_23	02_09		02_05 02_11 02_14 02_15 02_20

FIGURE 1 | Mental strategies used during the first (NF S01) and the last (NF S10) NF training session, presented separately for each participant of the SMR (subject code in black font color) and Gamma group (subject code in gray font color).

After the first NF training session, all NF-naïve participants reported to use a specific mental strategy. After the tenth NF training session, four participants of the SMR group and one participant of the Gamma group reported to have no particular strategy any more. Based on the subjective reports after the last NF session, participants were split up in two groups for subsequent statistical analyses: Participants using mental strategies to control their own EEG activity (SMR strategy group: 2 males, 4 females; Gamma strategy group: 4 males, 5 females) and participants describing no specific mental strategy to control their own EEG activity after gaining some NF experience (SMR no strategy group: 3 males, 1 female; Gamma no strategy group: 1 male).

EEG DATA ANALYSIS

Data preprocessing and analysis were performed with the Brain Vision Analyzer software (version 2.01, Brain Products GmbH, Munich, Germany). Ocular artifacts such as eye blinks were manually rejected by visual inspection based on the information about EOG activity provided by the EOG channel. After ocular artifact correction, automated rejection of other EEG artifacts (e.g., muscles) was performed (Criteria for rejection: $>50.00\,\mu V$ voltage step per sampling point, absolute voltage value $>\pm 120.00\,\mu V$). All data points with artifacts were excluded from the EEG analysis (15% of data).

For the EEG data analysis, absolute SMR (12–15 Hz) and Gamma (40–43 Hz) band power was extracted by means of complex demodulation (Brain Products GmbH, 2009). The extracted power values were averaged over the whole artifact free training runs in one session. For statistical analyses and better comparability of the data, SMR and Gamma power values were *z*-transformed.

RESULTS

NEUROFEEDBACK PERFORMANCE: MENTAL STRATEGY vs. REPORTING NO SPECIFIC STRATEGY

SMR group

In order to investigate the effects of spontaneous mental strategies on SMR based NF performance, a 2 × 2 univariate repeated measures analysis of variance (ANOVA) with the between subject factor strategy group (strategy group vs. no strategy group) and the within-subject factor time (first vs. last NF training session) was applied for the dependent variable *z*-transformed SMR power values. The ANOVA revealed a significant main effect of time $[F_{(1,\,8)} = 8.81, p < 0.05, \eta^2 = 0.52]$ and a significant main effect of strategy group $[F_{(1,\,8)} = 7.69,\ p < 0.05,\ \eta^2 = 0.49]$. Overall, SMR was higher in the last ($M = 0.49$ *z*-score, $SD = 1.05$) compared to the first NF training session ($M = 0.05$ *z*-score, $SD = 0.93$), and the no strategy group ($M = 1.12$ *z*-score, $SD = 1.50$) showed higher SMR values than the strategy group ($M = -0.58$ z-score, $SD = 1.22$). Moreover, the interaction effect strategy group*time $[F_{(1,\,8)} = 7.41,\ p < 0.05,\ \eta^2 = 0.48]$ was significant, too. Posttests showed that the two strategy groups did not differ in their SMR power during the first NF training session [$t_{(8)} = -2.18$, *ns.*]. In contrast, during the last NF training session, participants reporting no specific strategy showed significant higher SMR power values than participants still using a specific mental strategy [$t_{(8)} = -3.15$, $p < 0.05$]. Furthermore, participants still using a specific mental strategy in the last NF training session showed no significant changes in SMR power between the first and the last training session [$t_{(5)} = -0.38$, *ns.*], whereas the no strategy group showed a trend toward an increased SMR power during the last compared to the first training session [$t_{(3)} = -2.46$, $p = 0.09$]. In **Figure 2**, means and standard deviations of z-transformed SMR power values during the first and last NF session are illustrated, separately for both groups.

In order to analyze the time course of SMR power over the ten training sessions in more detail, we conducted regression analyses separately for the strategy and the no strategy group (predictor variable = session number; dependent variable = z-transformed SMR power). For the no strategy group, the regression model was by trend significant [$F_{(1,\ 8)} = 3.34$, $p = 0.10$]. With this regression model, 27.09% of variance of SMR power over the training sessions can be explained. When analyzing the time course of SMR power over the ten sessions separately for each participant of the no strategy group, all of them (i.e., 100%) showed a positive regression slope of the learning curve. In contrast, the regression model for the strategy group was not significant. Furthermore, we compared the regression slopes of the learning curves over the ten NF sessions between the strategy group and the no strategy group. The no strategy group showed significant higher positive slopes ($M = 0.089$, $SD = 0.035$) than the strategy group ($M = 0.002$, $SD = 0.040$) [$t_{(8)} = -3.52$, $p < 0.01$]. In **Figure 3**, the NF performance over all ten NF training sessions (means and standard deviations) is depicted for both groups. The no strategy group shows a linear increase in SMR power over the ten training sessions, whereas the strategy group shows no prominent changes in SMR power over all training sessions.

Note that participants of the SMR group did not show any linear increase or decrease in Gamma power over the 10 NF training sessions.

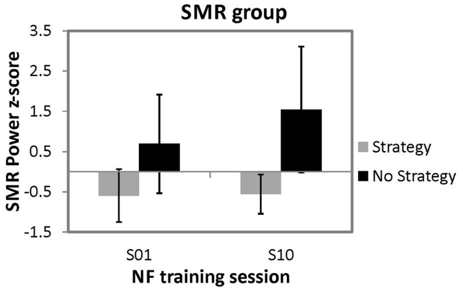


FIGURE 2 | Means and standard deviations of z-transformed SMR power (12–15 Hz) values during the first and tenth NF training session, presented separately for participants reporting to use a specific mental strategy in the tenth NF session (strategy group) and participants reporting no specific mental strategy in the tenth NF session (no strategy group).

Gamma group

To evaluate the effects of mental strategies on Gamma based NF performance, the same ANOVA as for the SMR group was applied for the dependent variable z-transformed Gamma power values. This ANOVA revealed no significant results. The results of the ANOVA should be interpreted with caution because only one participant formed the no strategy group. Therefore, we applied special t-tests comparing an individual's test score (single participant of the no strategy group) against norms derived from small samples (strategy group) (Crawford and Howell, 1998; Crawford and Garthwaite, 2002; Crawford et al., 2010). In the first [$t_{(8)} = -0.27$, *ns.*] and the last NF training session [$t_{(8)} = -0.52$, *ns.*] this single participant of the no strategy group did not differ significantly in his z-transformed Gamma values from the strategy group.

Furthermore, the same regression analyses were conducted as for the SMR group to examine the time course of Gamma power over the ten NF trainings. For the strategy group, this regression analyses did not reveal significant results. However, the regression model for the single participant of the no strategy group was significant by trend [$F_{(1,\ 8)} = 5.14$, $p = 0.05$]. 39.09% of variance in Gamma power could be explained by session number. In contrast to the no strategy group of the SMR NF training group, the single participant of the Gamma group that reported no specific mental strategy to increase Gamma power voluntarily showed a linear decrease in NF training performance over the ten sessions. When comparing the slope of the single participant reporting no strategy with the strategy group's slopes, no significant differences could be found [$t_{(8)} = -1.21$, *ns*]. (Crawford and Garthwaite, 2004). In **Figure 4**, the NF performance over all ten NF training sessions is depicted for both groups.

Participants of the Gamma group did not show any linear increase or decrease in SMR power over the 10 NF training sessions.

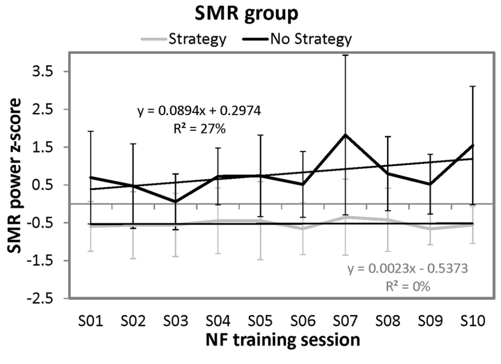


FIGURE 3 | Means and standard deviations of z-transformed SMR (12–15 Hz) power (NF performance) over the ten NF training sessions, presented separately for participants reporting to use a specific mental strategy in the tenth NF session (strategy group) and participants reporting no specific mental strategy in the tenth NF session (no strategy group) of the SMR group and the results of the regression analyses.

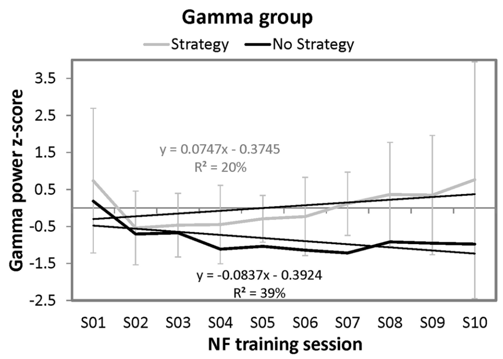


FIGURE 4 | Means and standard deviations of *z*-transformed Gamma (40–43 Hz) power (NF performance) over the ten NF training sessions, presented separately for participants reporting to use a specific mental strategy in the tenth NF session (strategy group) and participants reporting no specific mental strategy in the tenth NF session (no strategy group) of the Gamma group and the results of the regression analyses. Note that only standard deviations for the strategy group are plotted since only one participant was present in the no strategy group.

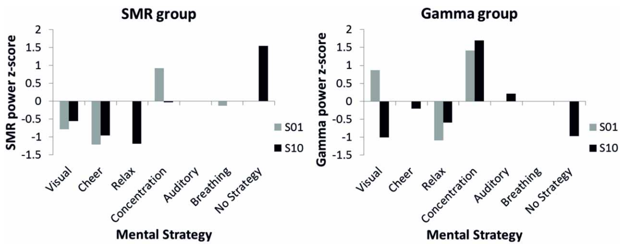


FIGURE 5 | *Z*-transformed SMR power for the SMR group (left panel) and *z*-transformed Gamma power for the Gamma group (right panel) during first (gray bars) and tenth (black bars) NF training session, presented separately for different mental strategies used to control one's own EEG signal. Note that no error bars are plotted since only single participants were present in several categories.

NEUROFEEDBACK PERFORMANCE: DIVERSE MENTAL STRATEGIES

The effects of the distinct mental strategies on the NF performance (SMR or Gamma power) are shown in **Figure 5**. In the first NF training session, where all participants reported using a mental strategy, for both the SMR and the Gamma group the most effective strategy seemed to be concentration. In the last NF training session, four participants of the SMR group reported to use no specific strategy any more to gain control over the EEG and six participants still described specific mental strategy in detail in the introspective report. The SMR based NF performance was highest in the no specific strategy condition during the last SMR based NF training session. In contrast, for the Gamma group reporting no specific mental strategy was not the most successful strategy to increase Gamma power voluntarily. The Gamma group was most successful when using the concentration strategy in both the first and the last NF session. Hence, the concentration strategy did not lead to a linear increase in Gamma power over the training sessions but rather to a constantly high Gamma power. The concentration strategy seems to be useful to increase SMR, too. SMR power was second highest for the concentration strategy in the tenth training session and highest during the first session. The relaxation strategy turned out to be the least effective mental strategy to increase SMR or Gamma power voluntarily. The breathing strategy was the second most effective in the first SMR based NF training session. However, nobody used this strategy at the end of the training.

DISCUSSION

The present work focused on the effects of spontaneous mental strategies used to control the EEG activity during NF training. NF users reported their spontaneous strategies to increase either their SMR (12–15 Hz) or Gamma (40–43 Hz) amplitude after the first and tenth NF training session. The usage of different mental strategies only affect SMR based NF performance but not Gamma related NF performance. After the first NF training session, all participants reported to use different types of mental strategies. After the last NF training session, some NF users reported no longer a particular strategy to control their SMR or Gamma power. In the SMR group, these participants showed a steadily increasing NF performance over ten NF training sessions. In contrast, participants still using a specific mental strategy in the last SMR based NF training session showed no significant improvements over the NF training sessions. Hence, our results show that different mental strategies have different effects on SMR based NF performance, but not on Gamma based NF performance. In the following paragraphs, these results are discussed in more detail.

In the first NF training session, all NF-naïve participants spontaneously verbalized a mental strategy to obtain control over their EEG power. This piece of evidence is in line with the assumption that learning to control one's own brain activity is associated with trial-and-error learning. By means of trial-and-error, the participants use diverse strategies and repeat them when positively reinforced (Curran and Stokes, 2003; Hammer et al., 2012). Though, after gaining some NF experience, four out of ten NF users of the SMR group and one participant of the Gamma group did not explicitly name any kind of specific mental strategy to control the feedback bar depicting their own EEG activity. This result is in line with the dual process theory (Lacroix and Gowen, 1981; Lacroix, 1986), which describes learning as an interaction of feed-forward and feed-back processes. In a first step, the NF user searches for an effective strategy. Therefore, all participants reported to use diverse mental strategies during the first NF session. After the NF user has found an effective strategy, this strategy will be maintained and improved and the strategy will become automatic. The learned skill to control the own SMR activity is stored in the implicit memory and its retrieval requires no consciousness any more (Strehl, 2013). Hence, those participants who did not report any specific mental strategy after the last NF session might have developed such an automatic mechanism. Nevertheless, it is also possible that the strategies verbalized by participants are not causally but only circumstantially connected with NF learning. Rather, the mechanisms to increase SMR becoming increasingly automatic during NF training may not correspond functionally to the content of the strategies verbalized. If this is correct, the role of explicit learning mechanisms in

NF may be more limited than that predicted by a dual process account.

To investigate the effects of spontaneous mental strategies on NF performance, participants of the SMR and Gamma group were divided into two sub-groups, respectively: one group of participants still using a specific mental strategy after ten NF training sessions, which was termed "strategy group," and participants who did not verbalize mental strategies after ten NF training sessions formed the second group, the so called "no strategy group." In the first NF training session, these two strategy groups did not differ significantly in their power values during the feedback training neither in the SMR nor in the Gamma group. This result seems to be obvious, because after the first session, all participants quoted that they have used a specific mental strategy during the NF training session. Hence, all participants spent cognitive resources and mental effort to gain control over their EEG signal. Consequently, SMR/Gamma power did not differ between the two strategy groups and the NF performance was comparable across subgroups during the first NF training session.

However, in the SMR group, the NF performance differed between the two strategy groups over the NF training course. The no strategy group showed a steady linear increase in SMR power over the ten NF training sessions as indicated by the regression analyses, which cannot be seen in the strategy group (**Figure 3**). During the last NF training session, participants reporting no particular strategy showed significantly higher SMR power values than participants reporting a specific mental strategy. Furthermore, participants still using a specific mental strategy in the last NF training session showed no significant changes in SMR power between the first and the last NF training session, whereas the no strategy group showed higher SMR power values at the end of the training compared to the first training session. These results further indicate that the no strategy group developed an automatic mechanism to control their SMR over the NF training sessions. Participants trying to control their SMR by using a specific mental strategy probably overload cognitive resources, which might be counterproductive in terms of increasing SMR power, since the sensorimotor rhythm in the EEG is associated with a state of physical relaxation and simultaneous mental focusing (Sterman, 1996, 2000; Nijboer et al., 2008; Serruya and Kahana, 2008). Prior NF studies investigating the effects of mental strategies on NF performance support our findings (Angelakis et al., 2007; Nan et al., 2012). Especially, Angelakis et al. (2007) reported on the positive effects of "thinking on nothing particular" on NF performance, which might be compatible with the "no strategy" technique used by some of our participants in the last NF training session. Although the participants of the no strategy group did not verbalize any specific mental strategy to gain control over their EEG, we do not know exactly what they were doing during the last NF training session to increase SMR. Did they have a totally "blank mind," or did they think on nothing particular, did they think on friends or something that had happened the day before? However, we do know that they did not spend too much effort in using different mental strategies, forcing to gain control over the own EEG. Probably, participants of the no strategy group automatized the skill of modulating the own EEG activity and therefore they did not need any specific mental strategies any more after repeated NF training sessions. This is in line with the assumption that the learned skill to successfully control the own SMR activity is stored in the implicit memory (Strehl, 2013). In contrast, participants that used a mental strategy described these strategies relatively detailed in the introspective report. This might also be a sign that participants of the strategy group spent too much mental effort and overloaded cognitive resources, leading to no improvements in SMR based NF performance.

Although not significant, the no strategy group presented a numerical advantage of about 1 z-score in SMR power in comparison to their peers from the strategy group in the first session of training (see **Figure 3**). This result might indicate that participants of the no strategy group have a predisposition to better up-regulate SMR activity. This predisposition manifests itself in two different ways: Firstly, participants of the no strategy group show higher levels of SMR power independently of training. Secondly, these same participants are more able to up-regulate their SMR power levels over the course of training. Moreover, these participants are also prone to report less explicit strategies after training, which might be indicative of stronger reliance upon implicit learning mechanisms largely independent of overt mental strategies. Further studies are needed to investigate the relation between the spontaneous use of mental strategies and SMR training success in more detail.

Importantly, not all mental strategies seem to be equally ineffective. In the first NF training session, where all participants verbalized a mental strategy, the most effective strategy seemed to be concentration. Hammer et al. (2012) also mentioned that the degree of concentration plays an important role in feedback studies. These authors found that the ability to concentrate on the feedback task is supportive for BCI performance because distracting stimuli can be better ignored. Furthermore, the authors speculate that performing a feedback task requires self-regulatory capacities to focus on and comply with the task despite possibly distracting thought (Hammer et al., 2012). Astonishingly, relaxation strategies turned out to be the least effective mental strategies to increase SMR power beside cheering and visual strategies. It is possible that the state of relaxation was reached anyway but in a less explicit and less controlled way. That the strategy to "relax" disappears from the focus of attention and from the focus of cognitive control employed may have helped that relaxation really happened. The breathing strategy was the second most effective in the first NF training session. However, nobody explicitly reported this strategy at the end of the training. Probably, the strategy of breathing consciously led to physical relaxation too, which might have increased SMR power. Summing up, looking at the effects of the different mental strategies on NF performance reveals that they have diverse effects. However, the most effective strategy to increase SMR voluntarily was not to be able no name anyone.

In sharp contrast, reports on spontaneous mental strategies had no specific effects on Gamma based NF training performance. In the Gamma group, only one participant reported to use no particular strategy any more to control the feedback bar during the last NF training session, which was counterproductive in terms of increasing Gamma power (see **Figure 4**). Hence, our findings do not support the findings by Keizer et al. (2010a,b) and Bird et al. (1978) who could show that people are able to modulate the power in the Gamma frequency band voluntarily (Bird et al., 1978; Keizer et al., 2010a,b; Rubik, 2011). Gamma power seems to be associated with meditative states, such as positive feelings of happiness, love, kindness, or compassion (Banquet, 1973; Lutz et al., 2004; Rubik, 2011). None of our participants reported to use such meditative mental strategies to modulate Gamma power voluntarily, which might be the reason why the Gamma group showed no changes in NF performance.

One critical issue in NF studies is the instruction provided by the experimenter (Lacroix and Gowen, 1981; Lacroix, 1986; Neuper et al., 2005; Hammer et al., 2012). In the present study, we did not prescribe any specific mental strategies which might be useful to control the feedback bars, as in the majority of NF studies. However, we gave our participants a minimal instruction, telling them to try to be mentally focused and physically relaxed during the NF training in order to increase their EEG amplitude (Leins et al., 2007; Serruya and Kahana, 2008). During the NF training sessions, participants regularly asked how to control their EEG voluntarily and if there are any useful strategies. But we did not give them any further instructions. Instructions given to the participants in prior NF studies are scarcely described. For instance, NF users were encouraged to look for themselves for appropriate strategies like physiological relaxation combined with positive mental activity (Raymond et al., 2005; Hoedlmoser et al., 2008; Gevensleben et al., 2009; Gruzelier et al., 2010; de Zambotti et al., 2012). Others explained the feedback loop and the rationale of the procedure in detail to their participants prior to taking part in the NF study (Vernon et al., 2003; Kropotov et al., 2005; Dempster and Vernon, 2009). In his NF review, Kropotov (2009) also addressed the question how to guide NF users to achieve the task in the most efficient way. He summarized that some practitioners prefer not to give any instructions to their participants by simply saying "Just do it." Others give instructions depending on the type of NF procedure: relaxation or activation (Kropotov, 2009).

In conclusion, in prior NF studies no standard instructions have been used. Our analyses of the spontaneous mental strategies used to control one's own brain activity revealed that participants are trying out diverse mental strategies at the beginning of the training. However, after gaining some NF experience, some participants do not verbalize specific mental strategies any more probably because of the development of automatic regulation skills. These participants are most successful in increasing SMR power voluntarily. Hence, we conclude that explicit instructions on how to control the feedback bar might be counterproductive in terms of impartiality and effortlessness during the training. Of course participants should be informed about the study process to some extent, but explaining the detailed feedback loop might stress participants too much since then they know how it should work theoretically. When these informed NF users are not successful from the beginning, they might become frustrated and probably start spending too much mental effort by using diverse mental strategies, and this may hamper performance and further learning. Hence, in accordance with our findings, we would suggest that the best instruction for future SMR based NF training studies is to tell the participants not trying too hard and to "just do it."

One important limitation of the current study is the sample size because it constrains the generalization of the present findings to other contexts. It is possible that other spontaneously verbalized strategies not occurring in the present study are more effective. Moreover, the contents of individual verbalizations were summarized using criteria defined *post-hoc* by the experimenter. To which extent the list of strategies spontaneously verbalized in NF studies has to be complemented is a question for future studies.

CONCLUSION

Here we show that mental strategies used to gain control over the own brain activity play an important role in successful NF performance, especially for SMR based NF performance. Distinct mental strategies have different effects on SMR based NF performance. However, not being able to name a specific one seems to be most effective, indicating the development of more automatic regulation mechanisms. More automatic processes seem to lead to a focused but relaxed mental state, which is beneficial when trying to increase SMR power voluntarily. These results have practical implications on future NF studies and provide guidelines for the instruction of NF users.

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APPENDIX

After the first and the last NF training session, participants wrote down the mental strategies they have used to control the feedback bars. Some of these introspective reports were very detailed descriptions of the used mental strategies, whereas others comprised only a few catchwords. In **Table A1**, these introspective reports are listed and the subsequent classification of these subjective descriptions into the different categories (visual strategies, auditory strategies, cheering strategies, relaxation, concentration, breathing, and no strategy) is specified, too. In most cases, the classification of the subjectively described strategies was unambiguous. However, when participants reported more than one strategy (e.g., participant 02_13, who reported visual strategies and relaxation in between) the most salient strategy was taken as background for the classification (e.g., for participant 02_13, the reported subjective strategy was categorized as visual strategy, since the visual strategy was more precisely described than the relaxation strategy).

Table A1 | Introspective reports of the used mental strategies to gain control over the feedback bars during the first (NF S01) and last (NF S10) neurofeedback training session, presented separately for each participant and the subsequent classification into the different strategy categories (visual strategies, auditory strategies, cheering strategies, relaxation, concentration, breathing, and no strategy).

Code	NF group	Mental strategy NF S01		Mental strategy NF S10	
		Introspective report	Categorization	Introspective report	Categorization
02_01	SMR	Visual imagination of a coffee cup standing on the bars on the left and the right side of the screen. The feedback bar in the middle of the screen was deemed as a roller blind.	Visual	Visual imagination of a green lawn, counting the reward points.	Visual
02_02	SMR	Issue commands on the bar in the middle of the screen.	Cheer	Cheering on the bars.	Cheer
02_03	Gamma	Fixation of the bar in the middle and trying to "switch off" any thoughts while total relaxation. Ignored bars on the left and the right side of the screen.	Relax	Cheering on the bars like cheering on the own kids.	Cheer
02_05	SMR	Changing between different levels of concentration, from very high to very low.	Concentration	No strategy used because any mental effort did not lead to successful results.	No strategy
02_06	SMR	Concentration on the bar in the middle of the screen.	Concentration	Concentration on the bar in the middle of the screen.	Concentration
02_07	Gamma	Visual focusing, visual lifting of the bar in the middle of the screen.	Visual	Visual focusing of a point on the screen.	Visual
02_08	Gamma	Concentration on the bar in the middle of the screen and ignoring the left and right bar.	Concentration	Concentration on the bar in the middle of the screen and ignoring the left and right bar.	Concentration
02_09	Gamma	Visual imagination of a specific scene of a movie (imagination of an actor and a ship being moved over a mountain).	Visual	Imagination of different music genres (except folk music).	Auditory
02_10	SMR	Fixation of bar in the middle of the screen and concentration on visual and auditory feedback.	Concentration	Concentration on the upper part of the bar in the middle of the screen.	Concentration
02_11	SMR	Visual focusing of the red and green bars on the screen to allow only green and no red bars.	Visual	No strategy used.	No strategy
02_13	SMR	Visually following the moving bar in the middle of the screen.	Visual	Visually focusing the moving bar in the middle of the screen and whenever this bar turned red for too long this bar was ignored. Relaxation in between.	Visual
02_14	SMR	Breathing to provide the brain with oxygen.	Breathing	No strategy used.	No strategy
02_15	SMR	Concentration.	Concentration	No strategy used.	No strategy
02_17	SMR	Visual imagery of different pictures, such as a growing tree, its roots, people around the tree and so on.	Visual	Relaxation.	Relax
02_18	Gamma	Relaxation.	Relax	Maximal relaxation and breathing consciously. Remembering baseline period.	Relax
02_19	Gamma	Concentration on forehead.	Concentration	Concentration on forehead.	Concentration
02_20	Gamma	Visual imagination.	Visual	No strategy used.	No strategy
02_21	Gamma	Concentration and focusing thoughts.	Concentration	Concentration on moving bars, focusing and breathing.	Concentration
02_22	Gamma	Concentration on the bar in the middle of the screen and ignoring the left and right bar.	Concentration	Concentration on the bar in the middle of the screen and sitting calm.	Concentration
02_23	Gamma	Concentration on the bar in the middle of the screen and focusing on its size.	Concentration	Concentration on the bar in the middle of the screen.	Concentration

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Improving the neural mechanisms of cognition through the pursuit of happiness

Karuna Subramaniam* and Sophia Vinogradov

Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

Edited by:
Guilherme Wood, Karl-Franzens-University of Graz, Austria

Reviewed by:
Shunsuke Kobayashi, Fukushima Medical University, Japan
Nicola Baumann, University of Trier, Germany

****Correspondence:***
Karuna Subramaniam, Department of Psychiatry, University of California, San Francisco, 513 Parnassus Avenue, S362, San Francisco, CA 94143, USA
e-mail: karuna.subramaniam@ucsf.edu

This paper reviews evidence on the neural basis of how positive mood states can modulate cognition, particularly during creative problem-solving. Studies performed over the past few decades demonstrate that individuals in a positive mood engage in a broader scope of attention, enhancing their access to distant and unusual semantic associations, and increasing task-shifting and problem-solving capacities. In this review, we summarize these behavioral studies; we then present recent findings on the changes in brain activation patterns that are induced by a positive mood when participants engage in problem-solving tasks and show how these relate to task performance. Additionally, we integrate findings on the neuromodulatory influence of positive mood on cognition as mediated by dopaminergic signaling in the prefrontal cortex and we describe how this system can go awry during pathological states of elevated mood as in mania. Finally, we describe current and future research directions using psychotherapeutic and real-time fMRI neurofeedback approaches to up-regulate positive mood and facilitate optimal creative cognitive performance. We conclude with some speculations on the clinical implications of this emerging area of research.

Keywords: positive mood, creative cognition, medial prefrontal cortex, fMRI, real-time fMRI

INTRODUCTION

Positive mood states—states of *happiness*—are the mental or emotional states of well-being characterized by positive emotions ranging from quiet contentment to intense joy (http://en.wikipedia.org/wiki/Happiness). When Abraham Lincoln said, "People are just as happy as they make up their minds to be," he was suggesting that happiness is a state of mind which to a certain extent is under our control. This is an important point since happiness is arguably the single most important factor for enhancing life satisfaction and success (Fredrickson, 2000). Happiness has been shown to be both the cause and consequence of success across various life domains including marriage, friendship, work performance, and overall health (Lyubomirsky et al., 2005; Sin and Lyubomirsky, 2009). For example, happiness is associated with better social interactions and higher work incomes (Lyubomirsky et al., 2005); better coping abilities (Moskowitz, 2010); health-related benefits (Moskowitz et al., 2008); self-beliefs of enhanced health, intelligence and social interactions (Myers and Diener, 1995); and greater personal resilience and overall well-being (Fredrickson, 2000, 2004). People in happy, positive mood states are better able to modulate cognition by enhancing broader thought-action repertoires, and demonstrate broadened attention, greater cognitive flexibility, and heightened creativity (Isen et al., 1985, 1987, 1991; Estrada et al., 1994; Fredrickson, 2004; Isen, 2005). Taken together, within the past three decades, studies from the positive psychology literature have revealed a plethora of behavioral evidence demonstrating that positive mood states contribute to life satisfaction and enhance certain aspects of cognitive performance.

Although the behavioral evidence of the interactions between positive mood and cognition is well-documented, there are very few studies that demonstrate how a positive mood can influence cognition at the neural systems level (e.g., Subramaniam et al., 2009). A deeper understanding of these neurobiological processes is critical, not just for understanding these mechanisms in healthy individuals, but for broadening our approach to the development of treatments for individuals with psychiatric illnesses that are often characterized by deficits in positive mood and cognition, such as people suffering from depressive disorders and schizophrenia.

BEHAVIORAL EVIDENCE DEMONSTRATES THAT POSITIVE MOOD MODULATES COGNITIVE OPERATIONS

Positive mood states facilitate a broad scope of attention (Gasper and Clore, 2002; Bolte et al., 2003) and enhance more integrative access to distant semantic associations (Isen et al., 1985; Federmeier et al., 2001; Friedman et al., 2003). This broader and more holistic mode of attention predicts and promotes cognitive control/flexibility, including flexible coping skills (Koestler, 1964; Aspinwall and Taylor, 1997) and creative solutions to problem-solving tasks (Isen et al., 1987; Rowe et al., 2007). Cognitive control is a multifaceted set of operations that includes the ability to inhibit dominant yet incorrect problem-solving paths and to switch between problem-solving strategies, and/or between broad and focused modes of attention. The result of increased cognitive control is that solvers are better able to select and act upon non-dominant yet correct solutions. A positive mood enhances these cognitive control processes by facilitating switching between broad and focused attentional modes (Baumann and Kuhl, 2005), and between different solving strategies (Dreisbach and Goschke, 2004), so that solvers are better able to reduce perseveration tendencies on errant problem-solving paths and increase selection of the correct solution (Ashby et al., 1999, 2002). Although the different studies described below induced positive mood in participants through various techniques, they all conducted objective mood manipulation measures to ensure that the target mood was induced and maintained. Together, the findings suggest that regardless of the mood induction method, a positive mood reliably enhances cognitive processes in distinct ways. We discuss each of these processes in more detail below.

POSITIVE MOOD FACILITATES A BROADENING SCOPE OF ATTENTION

Prior research suggests that a positive mood broadens the scope of attention, thoughts and actions (Fredrickson, 2001; Gasper and Clore, 2002; Bolte et al., 2003; Fredrickson and Branigan, 2005); this involves attending to more stimuli in both external visual space and internal semantic space, allowing access to more information to simultaneously influence solution efforts (Rowe et al., 2007). Furthermore, positive mood states are associated with greater global or holistic processing (i.e., seeing the forest before the trees) vs. local processing (i.e., seeing the trees before the forest). For example, Gasper and Clore (2002) induced positive and negative mood states by asking healthy participants to recall personal life events that made them feel either positive or negative. The mood manipulation check was effective; participants felt more positive and less negative after writing about a happy event. Subsequently, they measured mood-attention relationships with a visual matching test (see **Figure 1**, adapted from Kimchi and Palmer, 1982) in which participants were instructed to indicate which one of two sample figures looks most like a target figure. Each figure was either a square or a triangle (global feature) made up of smaller squares or triangles (local feature). Results revealed that positive mood participants were more likely to match the objects on the basis of global features than participants in a negative mood (Gasper and Clore, 2002). In a subsequent study, Fredrickson and Branigan (2005) replicated similar findings to the Gasper and Clore (2002), using an alternative mood induction technique of positive, neutral and negative film clips to induce the target mood state in healthy participants. When comparing participants' mood ratings to the film clips, Fredrickson and Branigan (2005) found that each film clip was effective at inducing the target mood state. They also found that after participants watched the positive films, they showed a significantly larger global bias on the global-local visual task when compared to the neutral mood participants, confirming their hypothesis that a positive mood broadens attention.

FIGURE 1 | Global-local task. One item from the global-local shape task [adapted with permission from Kimchi and Palmer (1982)]. Participants had to indicate which one of two sample figures most resembled the target figure (i.e., square made of squares). Each figure was either a square or a triangle (global feature) made up of smaller squares or triangles (local feature).

POSITIVE MOOD FACILITATES INTEGRATION AND ACCESS TO DISTANT SEMANTIC ASSOCIATIONS ACROSS A DIVERSE RANGE OF TASKS

Positive mood can also enhance integration processes, facilitating a broader access to remote semantic associations (Isen et al., 1987; Estrada et al., 1997; Federmeier et al., 2001; Bolte et al., 2003), which, in turn, facilitates creative problem solving. Some examples of how a positive mood enhances integration processes arise from word association tasks. Isen et al. (1985) used several different mood induction methods to induce the target mood state in participants: in one experiment, they used affectively-valenced (positive, neutral, and negative) words; in another experiment, they used positive and neutral film clips; and in a third experiment they gave participants candy vs. no manipulation. After each of these mood induction methods, participants performed word-association tasks in which they were presented with a neutral word and were then required to respond with word associations that came to mind (Isen et al., 1985; Ashby et al., 1999). Regardless of the mood induction method, Isen et al. (1985) found that participants in a positive mood were more likely to respond with remote word associations compared to participants in a neutral mood. For example, the dominant interpretation of the word *pen* is a writing tool; neutral-mood participants were likely to respond with a high frequency associate, such as *pencil* or *paper*. However, participants in a positive mood also included remote interpretations of *pen* as a fenced enclosure, and were thus more likely to respond with associations such as barn or pig. Thus, in Ashby et al.'s (1999) connectionist model of cognitive set selection, a positive mood led to the selection of a broader set of remote associations, which is known to promote creative solving ability.

These beneficial effects of a positive mood on enhancing integration processes across a broad set of semantic associations has been demonstrated many times, using a diverse range of tasks and populations—from college students doing word association and creative problem-solving tasks, to industrialists engaging in negotiations, to doctors integrating non-dominant yet relevant information earlier while solving medical cases (Carnevale and Isen, 1986; Isen et al., 1987; Estrada et al., 1994, 1997; Rowe et al., 2007). For example, when a positive mood was induced in doctors by giving them candy, they integrated non-dominant remote information earlier when solving a rare case of chronic hepatitis, as compared to controls in a neutral mood (Estrada et al., 1997). This positive mood-induced access to a broader range of associations and thoughts appears to facilitate cognitive control and creative problem-solving across a range of tasks (Isen et al., 1987; Baumann and Kuhl, 2002; Bolte et al., 2003; Fredrickson, 2004).

POSITIVE MOOD FACILITATES COGNITIVE CONTROL PROCESSES INVOLVED IN TASK SWITCHING AND RESPONSE SELECTION

In addition to broadening attention and promoting access to distant semantic associations, positive mood also facilitates creative problem solving by facilitating task switching and response selection. The remote association task (RAT) was created by Mednick (1962) to investigate specific aspects of cognitive control and creative problem solving. The RAT consists of presenting three seemingly unrelated words that are associated with a third solution word in different ways. For instance, the words: TENNIS, STICK and SAME are associated with the solution word MATCH by formation of a compound word (matchstick), by semantic association (tennis match), and by synonymy (same = match). The RAT task requires both broad divergent thinking and more focused convergent thinking. During broad divergent thinking, solvers need to access a wide set of associations (i.e., association words for TENNIS include: GAME, RACKET, BALL, COURT, SET, PLAYER, MATCH). During focused convergent thinking, solvers need to integrate distant semantic associations in different ways to find the correct meaningful solution (i.e., of all the associations, only MATCH fits with the words: TENNIS, STICK and SAME). Several groups have shown that on Mednick's creative RAT, participants in a positive mood state produced more solutions compared to controls in a neutral or negative mood, both in a sample of college students as well as in practicing physicians (Isen et al., 1987; Estrada et al., 1994; Rowe et al., 2007).

We modified Mednick's (1962) RAT task into a simpler version called the Compound Remote Association (CRA) task in which the solution word has to form a compound word or phrase with each of the three target words (Subramaniam et al., 2009). In the CRA task, the solver is given 3 words such as "tooth," "potato," and "heart" and is asked to think of a fourth word that can be combined with all three to form a compound word or phrase. The solution word can be placed either before or after any of the three words in the triad to form the compound word. In this case, "sweet" is the solution word, which forms the compounds "sweet-tooth" "sweet-potato," and "sweetheart." In the CRA task, when participants see the word "tooth" they need to inhibit the dominant association "ache" or "pain" when they realize that pain does not fit with potato (i.e., "potato-pain?"), and must switch to select an alternative non-dominant solution (i.e., "sweet" forming sweet-tooth, sweet-potato, and sweetheart). These problems are typically associated with insightful solutions, in which participants have an "Aha!" or "Eureka" experience during solution success.

Insightful problem solving requires engagement of cognitive control mechanisms involved in task switching and alternate response selection because there is frequently an impasse where solvers feel stuck, and believe they are making no progress toward the solution. To overcome this impasse, solvers need to inhibit prepotent albeit irrelevant associations in order to allow access and integration of remote yet solution-relevant concepts. Solvers are then able to suddenly recognize connections that had previously eluded them, and instantly see the solution in a new light in the "Eureka!" experience. Therefore, insightful problem-solving requires inhibition of task-irrelevant but prepotent responses, as well as task-switching to broader but non-dominant solution-relevant associations (Subramaniam et al., 2009).

We found that healthy college students higher in assessed positive mood (assessed with the Positive Affect Negative Affect Scale immediately prior to the experiment) solved more CRA problems overall, and specifically solved more CRA problems with insight, compared to college students lower in assessed positive mood. We also found that a positive mood was associated with increased brain activity in the medial prefrontal region during a preparatory interval preceding each solved problem. A positive mood was correlated with stronger preparatory signal that led to insight vs. analytical solutions, thus biasing participants toward insightful problem-solving; it appears that increased mPFC activity was associated with greater prefrontal cognitive control, which in turn allowed solvers to switch between broad attentional modes (required for detection of distant remote solution candidates) and focused attention for response selection (required to converge upon the correct solution).

Consistent with this interpretation, Baumann and Kuhl (2005) demonstrated that participants in a positive mood showed greater cognitive control in a global-local shape detection task (see **Figure 2**). In **Figure 2**, for the item on the left, the target "circle" is presented on a local dimension, but is presented on a global dimension for the item on the right. In order to induce the target mood state, participants were asked to recall personal experiences that felt positive or negative, and were then asked to note down positive, neutral, and negative words which reminded them of their past experiences. Participants were then given a self-generated prime-word (i.e., either positive, neutral or negative), which was then followed by the global-local shape task. When participants were in a positive vs. a neutral or negative mood, they responded faster to targets presented on a local dimension when the task necessitated local-feature detection. As such, they showed increased cognitive control by overcoming a global precedence in order to respond to non-dominant local features (i.e., detecting the circles that make up the triangle). In contrast, participants in a negative mood had slower response

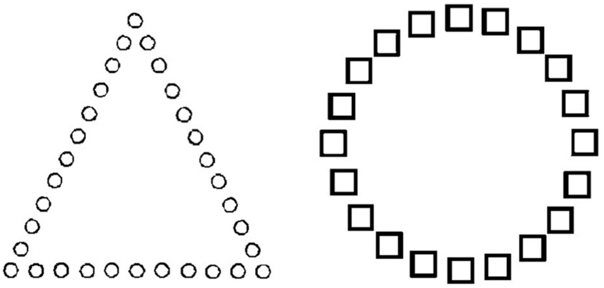


FIGURE 2 | Global-local task of cognitive control. For the item on the left, the circle is the target, presented on a local dimension. For the item on the right, the target circle is presented on a global dimension [reproduced with permission from Baumann and Kuhl (2005)]. Participants in a positive mood demonstrated increased cognitive control by responding to non-dominant local features (i.e., detecting the target circles that made up the triangle).

times to local targets when compared to a neutral mood. These results suggest that participants in a negative mood state had less cognitive flexibility, and thus were slower in switching to a non-prepotent local mode of processing from the default global mode of processing.

Switching can occur between global and local modes of attention, and also between strategies (Dreisbach and Goschke, 2004; Baumann and Kuhl, 2005). Prior research has shown that a positive mood enhances switching between different perspectives (Isen and Daubman, 1984; Isen, 2005). A shift from a focused local to a global attentional state increases the scope of semantic and visual access, which can promote enhanced selection of solution-relevant responses on classic insight problems such as Duncker's candle task (Duncker and Lees, 1945). Participants watched either a comedy film clip or a neutral film clip to induce the target mood state, followed by a word-rating scale to verify the efficacy of the mood manipulation. Following the manipulation check, participants were asked to solve Duncker's candle task. In this task, participants were presented with a box of tacks, a candle, and a book of matches and were asked to attach the candle to the wall in a way that it will burn without dripping wax on the table or floor. Participants in a positive vs. neutral mood were better able to shift their perspective from viewing the box as a container to viewing the box as a platform for the candle. Switching away from the prepotent view of perceiving the box as a container to viewing it as a platform facilitated solving when participants realized that the upright candle could be tacked from the matchbox to the wall (Isen et al., 1987). More recently, a positive mood has been shown to reduce perseveration and facilitate switching/shielding from distracters (Dreisbach and Goschke, 2004). It is important to note, however, that an optimal balance between task switching and task-shielding operations must be maintained in order to maximize creative problem-solving. A field of attention that is too broad, with far-ranging associations and a high degree of switching between solving strategies, can lead to increased distractibility, inhibiting solution selection. Similarly, a solver who maintains a very focused and narrow spotlight of attention, with little ability to switch away from unsuccessful strategies, will become "stuck" in a fruitless search for the solution.

MEDIAL PREFRONTAL NEURAL ACTIVATION IS A KEY COMPONENT OF THE INFLUENCE OF POSITIVE MOOD ON COGNITIVE PROCESSING

While a significant amount of research has been conducted on the neurobiology of reward (e.g., Beninger, 1991; Phillips et al., 1992; Knutson and Cooper, 2005; Cooper et al., 2009) and on the neural correlates of positive mood (e.g., Lane et al., 1998; Damasio et al., 2000; Habel et al., 2005; Burgdorf and Panksepp, 2006), only few studies have examined the neural system activation patterns mediating positive mood and cognition (Federmeier et al., 2001; Subramaniam et al., 2009, 2013).

Federmeier et al. (2001) used ERP to investigate the influence of positive mood on semantic relatedness. Mood was manipulated in each participant using positive and neutral photos from the International Affective Picture System. The effectiveness of the mood state induction was assessed with a written questionnaire asking participants to report on how much they liked the photos from each condition. Federmeier et al. (2001) found that a positive mood facilitated meaningful processing of distantly-related information, thus broadening semantic access and integration. Specifically, these investigators examined the N400 response, as an index of semantic relatedness on a sentence completion task. Participants read sentence pairs ending with either: (1) the most expected word, (2) an unexpected word from an expected semantic category, or (3) an unexpected word from a different (related) category. An example of a sentence was: "They wanted to make the hotel look more like a tropical resort. So, they planted rows of … " For the final word, (1) the most expected item, would be "palms"; (2) an unexpected item from the same semantic category would be "pines"; (3) and an unexpected item from a different semantic category would be "tulips." Following a positive mood induction vs. a neutral mood induction, participants showed a reduced N400 amplitude (indexing meaningful processing) for unexpected different category exemplars. Thus, a positive mood compared to a neutral mood specifically facilitated meaningful processing of distantly-related between-category exemplars. Subsequent studies have replicated the impact of positive mood on broadening the scope of semantic access (Rowe et al., 2007; Subramaniam et al., 2009). This suggests that a positive mood may facilitate integration processes by relaxing constraints to enhance both semantic distance as well as breadth of attention.

In an fMRI study using Compound Remote Associate (CRA) problems (Subramaniam et al., 2009), we found that participants who were higher in a positive mood state (assessed with the PANAS, immediately prior to the fMRI study) revealed greater ACC/mPFC activity during a preparation period prior to problem onset when compared to participants lower in a positive mood (see **Figure 3**). Increased mPFC activation prior to problem onset appears to represent an enhanced state of creative cognitive preparation, as it correlated with participants' overall solving ability, with insight solving and with positive mood. These data suggest that mPFC preparatory signal predisposed positive mood participants to solve more problems overall, and to specifically solve more of the problems using insight (Subramaniam et al., 2009). We also demonstrated, using EEG topography and frequency recordings that insight preparation

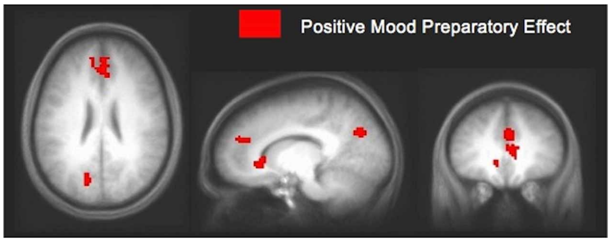


FIGURE 3 | Positive mood preparatory effect. Signal change in mPFC/ACC and posterior cingulate cortex during the preparation period for participants high in positive mood vs. participants low in positive mood, at a threshold of $p < 0.005$ (uncorrected). Increased mPFC signal enhanced cognitive preparation, predisposing positive mood participants to solve more problems overall, and to specifically solve more creatively with insight [adapted from Subramaniam et al. (2009)].

(i.e., preparatory brain states that bias and facilitate subsequent solving with insight), compared to step-by-step analytical preparation, involved increased activity over medial prefrontal regions (Kounios et al., 2006). Increased activation over medial prefrontal regions appeared to reflect increased preparation to exert top-down cognitive control mechanisms to switch cognitive strategies and select the correct solution. Additionally, insight compared to step-by-step analytical preparation also involved occipital alpha activation (which inversely relates to neural activity) thought to shield top-down processes from interference by bottom up visual stimulation (Kounios et al., 2006). Thus, a positive mood may predispose and facilitate creative cognition by enhancing activation within the medial prefrontal cortex, thus supporting the regulation of attention/cognitive control processes as the demands of the task necessitate. Creative insightful solutions may be facilitated by modulating the shift between task shielding effects (i.e., shown by visual occipital alpha activation during insight preparation) and task switching/selection effects (i.e., shown by increased activity over medial frontal regions). Enhanced cognitive control induced by a positive mood enables solvers to switch away from task-irrelevant distracters in order to select from a broader array of solution-relevant information.

In a subsequent fMRI study, we demonstrated that not only a positive mood, but also positive stimuli could enhance neural patterns associated with creative cognition (Subramaniam et al., 2013). We specifically examined how positive stimuli (i.e., positive words) could modulate creative metaphoric processing. A metaphor is a figure of speech in which a subject is compared to an unrelated object (i.e., *He is the apple of my eye*). Metaphoric comprehension is considered a type of creative cognition, and involves linking previously unassociated meanings in order to create a new understanding of one item in terms of another (in the example above, the "apple" refers to someone beloved). According to the Gradient Salience Hypothesis (Giora, 1997, 2003), metaphoric processing is modulated by the conventionality, frequency, and familiarity of the words. We investigated neural processes associated with conventional (familiar) metaphors (e.g., *brain freeze*) as well as novel (unfamiliar) metaphors (e.g., *unfenced idea*). Conventional metaphoric processing involves recalling a familiar closely-connected meaning (Amanzio et al., 2008). By contrast, novel metaphoric processing is a type of creative cognition that involves formulating new meanings from unfamiliar expressions that have not been previously encountered (Subramaniam et al., 2012a).

In our metaphor study (Subramaniam et al., 2013), prior to fMRI scanning, participants received a list of word pairs (novel unfamiliar metaphors, conventional familiar metaphors, and unrelated meaningless words) and were asked to denote the valence (positive, negative, or neutral) of each word pair. For example, conventional familiar metaphors such as "beautiful mind," "visual field," and "sour grapes" were typically classified as having positive, neutral and negative connotations, respectively. Similarly, novel unfamiliar metaphors such as "joy bits," "memory phantoms" and "caged cry" were also typically classified as having positive, neutral, and negative connotations. During fMRI scanning, participants had to decide whether the word pairs formed meaningful or meaningless expressions.

We found that participants made more accurate meaningful judgments when viewing metaphors that were positively-valenced, and that this was associated with enhanced modulation of the mPFC. The mPFC was activated during positively-valenced metaphors in general, but revealed most activation specifically when participants viewed positively-valenced novel metaphors (see **Figure 4**). We hypothesize that increased mPFC signal for positively-valenced novel metaphors (which may also have induced a positive mood reaction) enabled participants to have a broader scope of attention that facilitated access to a broad array of different possible semantic interpretations for the unfamiliar word pairs. Greater mPFC modulation may also have enabled participants to exert greater cognitive control to eliminate, or switch away, from meaningless interpretations. In this way, participants were better able to select the correct interpretation that linked the novel words together in a meaningful way.

We do not mean to imply that the observed activations in the medial prefrontal cortex (mPFC) represents a neural correlate of positive mood, nor that positive mood states will always benefit cognition. We also do not mean to suggest that the mPFC is the only brain region which mediates positive mood-cognition interactions. Indeed, other regions such as the basal ganglia—that are central to both cognition (McNab and Klingberg, 2008) and reward processes (Knutson and Cooper, 2005)—are also important in mood-cognition interactions. However, our data do indicate that positive mood enhances activity in the rostral dACC/mPFC, and that increased activation in this region (even prior to the onset of a problem) is

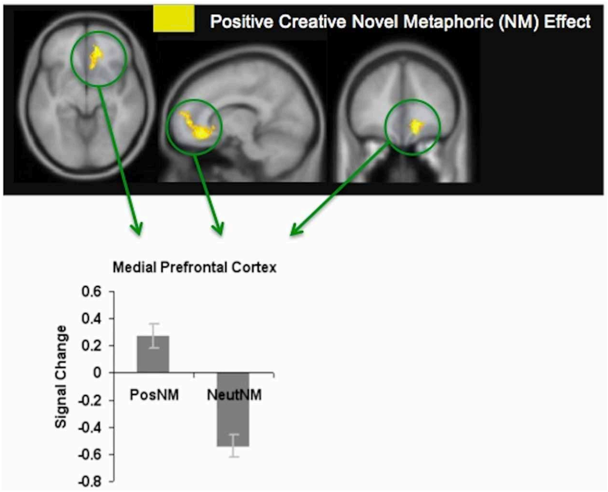


FIGURE 4 | Positive creative novel metaphoric effect. Signal change for positively-valenced creative novel metaphors (PosNM) vs. neutral novel metaphors (NeutNM) at a threshold of $p < 0.001$ (uncorrected). Mean mPFC signal (beta weights) for each condition is revealed in the bar chart [adapted from Subramaniam et al. (2013)].

significantly correlated with improved creative cognitive solving abilities.

DOPAMINERGIC NEUROMODULATION PLAYS AN IMPORTANT ROLE IN THE RELATIONSHIP OF POSITIVE MOOD TO COGNITION

Some of the earliest investigators in this field proposed that the cognitive effects of positive mood were likely to be mediated by increased dopaminergic release in the brain (Ashby et al., 1999, 2002). Ashby et al.'s (1999, 2002) predictions were informed by research on the neurobiology of reward processing, which is associated with increased positive mood and phasic release of dopamine (Beninger, 1991; Bozarth, 1991; Phillips et al., 1992; Schultz, 1992). They predicted that increased dopamine tone in prefrontal cortex induced by a positive mood would enhance access to a broad range of associations and facilitate switching between attentional modes/strategies. Indeed, prior research suggests that such increases of dopamine in the prefrontal cortex up-regulate cognitive control mechanisms (Braver et al., 1999). However, we must emphasize that the relationship between positive mood, reward processing, dopamine neuromodulation, and cognitive control is likely to be highly non-linear and complex. Studies from animals and humans reveal that the prediction and receipt of rewards is associated with phasic activation of midbrain dopaminergic firing, while a positive mood is associated with overall increased prefrontal dopamine release each with distinct implications for cognition (Ashby et al., 2002; Schultz, 2002; Montgomery et al., 2007). As this field is still in its early stages, we present here only a brief overview and a proposed model for the role of dopaminergic modulation in the cognitive effects of positive mood, in order to stimulate further research.

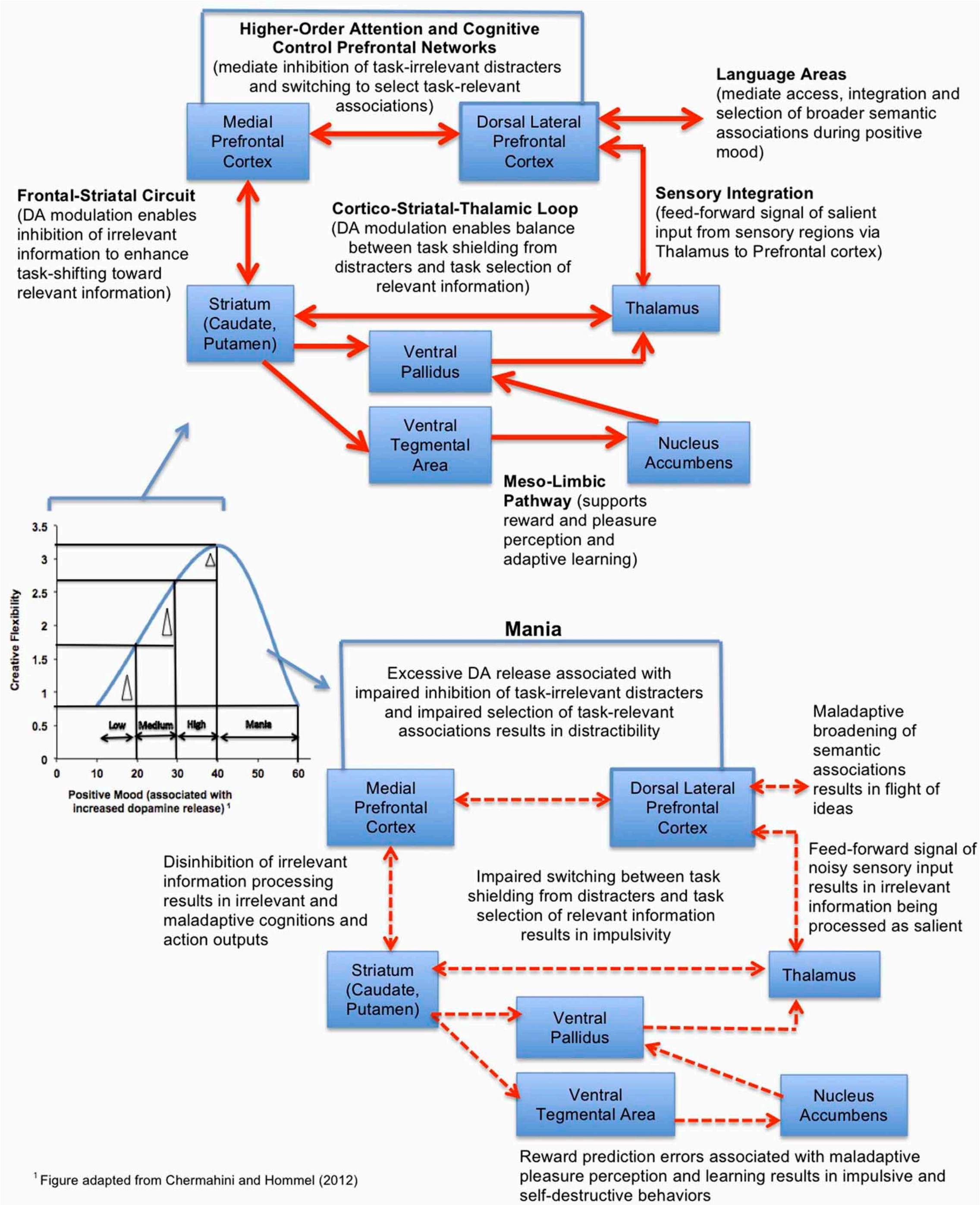
First, while a positive mood facilitates creativity on tasks that require divergent (broad) thinking, it is important to note that Rowe et al. (2007) demonstrated that a positive mood may not be beneficial for tasks requiring focused attention. This finding raises the question of whether there is an optimal mood specific to the demands of the task at hand. Specifically, Rowe et al. (2007) used positive and sad music to induce positive and negative mood states, relative to the neutral condition (which was induced by participants reading facts about Canada); a mood manipulation check demonstrated that the mood induction was successful. Participants were then tested on the Eriksen flanker task in which they had to selectively attend to the central letter while ignoring distracting flanker stimuli. Rowe et al. (2007) found that positive mood states increased participants' visual scope of attention, making them more susceptible to the flanker distracters. Participants who had greatest visuospatial breadth (increased susceptibility to the flanker distracters) also showed greatest breadth in semantic scope of attention (indexed by the number of remote associates accessed on the Remote Associates Task). Thus, while a positive mood does broaden attention both in terms of internal conceptual semantic associations and external visual space, it does not necessarily improve all aspects of cognitive performance.

Chermahini and Hommel (2012) investigated this question more closely by examining the relationship between positive mood, creativity, and dopamine on a creative divergent thinking task. They found that performance on a divergent thinking task was associated with spontaneous eye-blink rates (an indirect measure of an individual's central dopamine tone), following an inverted U-shape. The results suggest that greatest cognitive flexibility is reached at an optimal level ("sweet spot") of dopamine release. They next used mood manipulation techniques in conjunction with eye-blink rates (EBR) on this task to study the influence of a positive mood on EBR and creative divergent thinking. Mood was manipulated through mental recall in which participants were asked to write down and recall positive and negative personal events in their life that made them happy or sad. The mood manipulation check confirmed that participants were more happy after the positive mood induction than before, and were less happy after the negative mood induction than before. EBRs were recorded right after the mood induction. Participants then performed an Alternate Uses Task used to assess divergent thinking. In this task, they were given a household item such as a cup, and were asked to write down as many possible uses for it in 5 min.

The investigators found that the positive mood induction increased EBR and increased flexibility on the divergent thinking task compared to baseline. The more positive participants became, the more flexible they were on the divergent thinking task and the more their EBRs increased. These results indicate that the changes in EBR (indexing central dopamine levels) induced by a positive mood were related to the increases in flexibility. This relationship was not found for the negative mood condition. Interestingly, upon closer inspection, when the investigators conducted a median split of EBR at baseline, they found that the induction of a positive mood improved flexibility in the low-EBR group only. These data indicate that the relationship between positive mood, dopamine tone, and creative problem-solving is non-linear, and suggest that positive mood induction methods might have the most cognitive impact on individuals who have low basal dopamine tone.

To extend upon Chermahini and Hommel's (2012) study, we propose a working model (see **Figure 5**), in which positive mood induction methods would have the greatest cognitive benefit on tasks which require a broad scope of attention and particularly for individuals with low-medium basal positive mood levels (and also, theoretically, lower prefrontal dopamine tone), moving these individuals toward an optimal level of cognitive flexibility. In individuals with high basal positive mood levels, the cognitive benefit will be smaller. In light of the evidence so far, we tentatively propose that positive mood inductions associated with increased dopamine release in the prefrontal cortex will help the lower-mood individuals achieve improved cognitive control operations related to task-switching and response selection (Cohen and Servan-Schreiber, 1992; Cohen et al., 1996), which are essential components of creativity. These beneficial cognitive effects will be maximized on tasks that require a broader scope of attention (Dreisbach and Goschke, 2004; Rowe et al., 2007).

By contrast, positive mood inductions in individuals with abnormally high states of elevated mood, such as occurs during a manic episode, would be contraindicated, as this would contribute to further impairment in already impaired cognitive control processes (**Figure 5**). Individuals suffering from mania



[1] Figure adapted from Chermahini and Hommel (2012)

FIGURE 5 | Model of the neural system interactions mediating the effect of positive mood on creative cognition. The model predicts that the largest gains in cognitive flexibility (indicated by the delta triangle) induced by positive mood inductions will be observed for subjects with low-medium basal positive mood levels, while individuals with mania will have impaired creative flexibility.

are known to show weakened prefrontal control (Morice, 1990; Johnson, 2005), and it is theorized that hyperdopaminergic tone in prefrontal cortex during mania is associated with disinhibition in fronto-striatal efferents, contributing to a "noisy signal" that impairs the selection of task-relevant information (Swerdlow and Koob, 1987; Diehl and Gershon, 1992). Noisy signal from fronto-striatal efferents into the mesolimbic pathway contributes to reward-prediction errors, such that manic individuals have difficulty distinguishing behaviorally salient and adaptive rewarding stimuli from less salient stimuli (Abler et al., 2008). Consequently, mania is associated with an overly broad scope of attention, "hyper-salience," distractibility, flight of ideas, and impaired decision-making (Clark et al., 2002)—suggesting again that there is a U-shaped curve—"too much" dopamine tone in prefrontal regions can be as deleterious to adaptive creative problem-solving as too little (Murphy et al., 1999, 2001). In this light, it is interesting that mania—at least in its early phases of hypomania—is characterized by broad and creative semantic associations and thought processes, as well as high creative output, suggesting that there may be an optimal level of prefrontal dopamine release required for maximal creative performance (Schuldberg, 1990; Jamison, 1993; Kaufmann, 2003) (**Figure 5**).

BEHAVIORAL INTERVENTIONS CAN BE USED TO IMPROVE POSITIVE MOOD AND ENHANCE COGNITION

A number of behavioral interventions have been developed from the "positive psychology" model, and include: practicing optimistic thinking, increasing attention and memory of positive stimuli and experiences, practicing mindfulness and acceptance, and increasing socializing behaviors. Sin and Lyubomirsky (2009) conducted a meta-analysis of 49 positive psychology interventions, and found that they were highly effective in enhancing positive mood and overall well-being, with a medium effect size of.29. Additionally, such positive psychology interventions enhance mood and well-being not only in healthy participants, but also in a range of patient populations, including those suffering from depression, anxiety, schizophrenia and HIV (Fava et al., 2005; Seligman et al., 2006; Moskowitz et al., 2012; Meyer et al., 2012; Caponigro et al., 2013). While the cognitive and underlying neural effects of these interventions are not yet known, this represents a fruitful area of future investigation.

In the past few years, a novel approach to positive mood interventions has emerged which allows for participants to volitionally up-regulate positive mood states via neurofeedback techniques such as real-time fMRI. Participants can be trained to voluntarily control neural fMRI signal from target regions implicated in positive emotional processes (Johnston et al., 2010, 2011). Though it has not yet been studied, positive mood up-regulation using neurofeedback is likely to modulate cognition, particularly creative cognition. Based on our prior findings (Subramaniam et al., 2009), we would predict that participants who are trained to up-regulate signal within mPFC and bilateral lateral prefrontal cortices will show enhanced positive mood preparatory brain states. These enhanced positive mood preparatory brain states are likely to facilitate attention/cognitive control processes on creative tasks.

It is possible that real-time fMRI neurofeedback techniques could be used to enhance positive mood and cognition not only in healthy individuals, but also in individuals with depression and schizophrenia who are characterized as having both reduced sensitivity for maintaining positive affect and experiences in memory as well as heightened sensitivity to negative stimuli (Sloan et al., 1997; Kan et al., 2004; Gard et al., 2011; Holt et al., 2011; Ursu et al., 2011). Interestingly, in patients with depression and schizophrenia, impaired attention, memory, self-regulation and cognitive control associated with reduced cingulate/prefrontal activation, has shown to be reversed with stimulation or enhanced activation in these regions (Pascual-Leone et al., 1996; Mayberg et al., 2005; Haut et al., 2010; Subramaniam et al., 2012b). Thus, it is possible that real-time fMRI neurofeedback targeting the anterior cingulate and medial prefrontal cortex may enhance positive mood-cognition interactions in such patient groups.

SEVERAL CAVEATS

While we have argued in this review that positive mood exerts some specific effects on neural activation states, in turn influencing cognitive processes, it is important to stop and consider whether other possible mechanisms might explain the effects of positive mood on cognition. For example, could the cognitive-enhancing influence of a positive mood be simply due to the non-specific effects of physiologic arousal? To test this, Isen et al. (1987) performed a study that included participants engaging in exercise (to generate arousal with no affective tone), along with a positive mood group, a neutral mood group, and a negative mood group. This study found that participants in the exercise condition did not demonstrate more solutions on classical insight problems, such as Duncker's candle task, compared to the neutral or negative mood condition; in contrast, the positive mood group produced more solutions than any of the other groups. These findings suggest that the influence of positive mood on cognitive control/flexibility is not simply due to physiologic arousal.

Other investigators have proposed that a positive mood facilitates a more heuristic, superficial mode of processing. For instance, positive mood participants have been suggested to use "satisfising" and superficial, rather than optimizing solving strategies (Kaufmann and Vosburg, 1997). Estrada et al. (1997) found evidence to the contrary while observing physicians in a positive mood state decide on a diagnosis for a rare case of liver disease. Physicians in this study showed no evidence of superficial processing, defined as deciding on a diagnosis without having enough evidence. Furthermore, we have argued previously that superficial processing induced by a positive mood would lead to more premature and incorrect responses; yet, high and low positive-mood participants made equally few errors on our creative problem-solving task (Subramaniam et al., 2009). Therefore, it appears that the nature of the task is important, and that one cannot make generalized conclusions about mood-cognition interactions without taking the specific task and event/contrast of interest into account. It is possible, for example, that positive mood participants may engage in more superficial processing on certain tasks compared to neutral mood participants simply because they find the task boring or incompatible with their mood state. Finally, some researchers have proposed that a positive mood reduces overall cognitive capacity (Mackie and Worth, 1989). For instance, a positive mood may increase the load on working memory because it increases the occurrence of positive mood-related thoughts that are more likely to interrupt cognitive processing (Seibert and Ellis, 1991). The evidence for this assertion does not appear to be strong, however; and again, it is likely that the demands of the task (selective focused attention vs. broad task-switching or interference resolution) play an important role in determining the ultimate cognitive outcomes of a positive mood state.

Another caveat in terms of the existing literature is the chicken-and-egg question of which mechanisms are primary and which are secondary. Does adopting a positive mood state induce increased dopaminergic tone in prefrontal regions and enhance access to distant semantic associations? Or do individuals with broader and more rapidly accessible semantic association networks tend to exhibit positive mood states? Or are both of these phenomena— a certain *joie de vivre* plus rapidly spreading access in semantic networks—the manifestation of some other primary underlying neural signature (e.g., dopaminergic tone in striatal and prefrontal neural systems)? Only carefully designed mood-induction studies, as well as probes into mood, reward responsivity, and creative problem-solving across different behavioral phenotypes, can answer these questions.

We also need to add a word of caution about potential clinical applications. It may very well be the case that inducing a positive mood with the goal of enhancing more far-ranging semantic associations could be deleterious in the case of people predisposed to mania or to schizophrenia. In the former, one might precipitate an actual manic episode (as can happen when such people are treated with antidepressants). In the latter, one might worsen symptoms of thought disorder, since some forms of schizophrenia are in fact characterized by the presence of too many broad and maladaptive associations. Sometimes, too much "creativity" can be deleterious.

It is highly likely that people can learn—through a variety of methods—to increase their positive mood volitionally, using a range of straightforward behavioral techniques, and also through real-time fMRI neurofeedback. The question will be: For whom are these approaches most beneficial? And how should they be combined with other approaches in order to maximize healthy functioning and well-being? Enhancing broader semantic associations and greater cognitive flexibility may be very useful for a person with cocaine addiction who is in an active treatment program learning new critical psychosocial skills, but may be very maladaptive for the same individual when they are in their "using" environment. A depressed individual with low motivation and many perseverative ruminations about past failures may benefit greatly from mood enhancement that broadens their scope of attention and facilitates examining alternative interpretations through cognitive behavioral therapy. But absent such psychological treatment, the same broadening of attention may lead the depressed individual to contemplate various methods of self-harm/suicide as a viable alternative.

SOME HAPPY THOUGHTS FOR THE FUTURE

We have entered a new era in our understanding of how to optimize learning in educational environments, and interestingly, it is an era that recognizes the importance of developing creative problem-solving capacities, rather than simply drilling the rote memorization of facts and figures. We now understand that critical learning occurs best in social contexts, under conditions of high intrinsic motivation, and is facilitated by appropriate rewards—all conditions that generate and sustain positive mood states. In the coming years, we can look forward to an even more knowledgeable and nuanced grasp of how to use these positive moods to help learners develop their skills as innovative and creative problem-solvers.

Similarly, there is a sea change in our approach to facilitating health and well-being in individuals with psychiatric illness. In the past decade, the field of mental health treatment has embraced a model of autonomy, dignity, and recovery for people with psychiatric illness; this has generated a growing emphasis on preventive interventions, on the techniques of positive psychology, and on developing therapies that go beyond the palliation of symptoms and that instead generate optimal well-being and community functioning. With a new focus on the important role that expectation and motivation play in the recovery process, and with a greater understanding of the many behavioral elements that can induce positive changes in mood state, we can expect to become even more refined in our ability to create mood-enhancing interventions to help individuals engage in adaptive problem-solving and creative skill-learning and coping.

Finally, the nascent but rapidly growing area of computerized cognitive training for psychiatric illnesses is moving in the direction of "gamification"—adapting the techniques of game developers and interactive software experts to make the cognitive training as engaging, fun, and rewarding as possible (Vinogradov et al., 2012). Such a treatment approach, if it reaches its full potential, will be able to harness the mood-elevating aspects of well-designed games and of social networking to promote the highest possible degree of cognitive enhancement and learning. The ultimate aim will be to help all individuals maximize their "happiness" and "creative problem-solving" potential, so they can—to paraphrase Lincoln—make up their minds to be as happy and successful as possible.

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Empathy, motivation, and P300-BCI performance

Sonja C. Kleih* and Andrea Kübler

Department of Psychology, University of Würzburg, Würzburg, Germany

Edited by:
Elisabeth V. C. Friedrich, University of Graz, Austria

Reviewed by:
Robert Leeb, Ecole Polytechnique Fédérale de Lausanne, Switzerland
Silvia Erika Kober, University of Graz, Austria

****Correspondence:***
Sonja C. Kleih, Department of Psychology, University of Würzburg, Marcusstrasse 9-11, 97070 Würzburg, Germany
e-mail: sonja.kleih@uni-wuerzburg.de

Motivation moderately influences brain–computer interface (BCI) performance in healthy subjects when monetary reward is used to manipulate extrinsic motivation. However, the motivation of severely paralyzed patients, who are potentially in need for BCI, could mainly be internal and thus, an intrinsic motivator may be more powerful. Also healthy subjects who participate in BCI studies could be internally motivated as they may wish to contribute to research and thus extrinsic motivation by monetary reward would be less important than the content of the study. In this respect, motivation could be defined as "motivation-to-help." The aim of this study was to investigate, whether subjects with high motivation for helping and who are highly empathic would perform better with a BCI controlled by event-related potentials (P300-BCI). We included $N = 20$ healthy young participants naïve to BCI and grouped them according to their motivation for participating in a BCI study in a low and highly motivated group. Motivation was further manipulated with interesting or boring presentations about BCI and the possibility to help patients. Motivation for helping did neither influence BCI performance nor the P300 amplitude. Post hoc, subjects were re-grouped according to their ability for perspective taking. We found significantly higher P300 amplitudes on parietal electrodes in participants with a low ability for perspective taking and therefore, lower empathy, as compared to participants with higher empathy. The lack of an effect of motivation on BCI performance contradicts previous findings and thus, requires further investigation. We speculate that subjects with higher empathy who are good perspective takers with regards to patients in potential need of BCI, may be more emotionally involved and therefore, less able to allocate attention on the BCI task at hand.

Keywords: brain–computer interface, motivation, empathy, ERP, P300, psychological variables

INTRODUCTION

One goal of brain–computer interface (BCI) research is to support people with severe motor impairment who need assisted communication (Kübler and Müller, 2007). Event-related potentials (ERPs) are amongst the most efficacious input signals for BCI (Sellers et al., 2012), which are elicited after presentation of a rare stimulus (oddball) in a stream of frequent non-target stimuli (Sutton et al., 1965). In such an ERP-based BCI the user has to focus attention on the target stimulus presented either in a row or a column of a character matrix (Farwell and Donchin, 1988). In the classic P300-BCI, all rows and columns of a letter or item matrix are flashed in random order (one sequence), therefore a target character is only flashed twice in one sequence (once in the row and once in the column) while the non-target characters are flashed several times. The target character constitutes an oddball which elicits ERPs, mainly a positive potential 300 ms after stimulus presentation (P300; Sutton et al., 1965). Attention allocation increases the P300 amplitude which is also influenced by the value of the target stimulus (Johnson, 1986).

Even though BCI researchers often claim to aim at providing assistive communication for people with severe motor impairment, BCI paradigms are usually tested with healthy volunteers. This is mostly because prior to involving patients in need who are difficult to reach and with who measurements are time and cost intensive, paradigms should be running flawlessly and possibly need to be improved after first experiences with healthy participants. For some healthy volunteers the knowledge about the goals of BCI research might be a more important reason for study participation than the offered monetary compensation. Those subjects may feel enthusiastic about contributing to further developments in BCI that could one day support communication in people with severe impairment. For others, monetary reward may be the main incentive for study participation. Thus, motivation may differ between these groups of potential study participants which in turn could have an effect on BCI performance.

It has been repeatedly shown that motivation affected BCI performance in healthy participants (Nijboer et al., 2008a,b; Kleih et al., 2011a,b; Käthner et al., 2013) and in severely paralyzed end-users (Nijboer et al., 2010). Manipulating motivation confirmed the proposed effect in healthy participants (Kleih et al., 2010) and end-users (Kleih and Kübler, in press). To date, in the context of P300-based BCI, motivation was manipulated with monetary reward (Kleih et al., 2010; Kleih and Kübler, in press) and it was shown that not the monetary reward had the strongest effect, but the motivation independent of such reward. As healthy subjects could earn at the most 50 Eurocents per correctly selected letter and subjects with motoneurone disease a gift certificate worth 20 Euro if they performed better in a second P300-BCI block than in the first, monetary rewards were small and thus, possibly not sufficiently salient. Both rewards might have been perceived as too low to increase motivation. Further, the effect of monetary reward on the P300 ERP may be weak. Consequently, in this paper we investigated whether a non-monetary motivation manipulation would affect the P300 amplitude and spelling success in a P300-based BCI.

To do so, we first sorted the participants in two groups according to their "motivation for helping" in a high and low motivated group. The motivation of the "highly motivated" group may be interpreted as "intrinsic" motivation (Deci and Ryan, 1985; Ryan and Deci, 2000). However, to be purely intrinsic, the reasons for study participation would have to be solely joy or altruism (Fehr and Fischbacher, 2003) which could both lead to a flow experience (Csikszentmihalyi and Csikszentmihalyi, 1992; Csikszentmihalyi and Charpentier, 2008). As soon as an action is performed because it leads to another goal, this action motivation would be categorized "extrinsic" because an action is not initiated by the action itself but by the consequences resulting from that action (Deci and Ryan, 1985; Ryan and Deci, 2000). Consequently, also for people who participate in BCI studies not only for monetary compensation or reward but also because they would like to support further development of assistive technology, motivation would be second goal extrinsic because severely disabled people may benefit in the future.

In motivation theory, participating in a study because one would like to contribute to research while also being interested in the monetary compensation translates to "introjected" or "identified regulation" as defined by the self determination theory (SDT; Ryan and Deci, 2000; see **Figure 1**). The SDT states that behavior ranges on a continuum from being completely non-self-determined to being entirely self-determined (see **Figure 1**). Perceived motivation, regulatory styles, and the perceived locus of control (PLOC) also differ according to the level of behavioral self-determination (see **Figure 1**). In the SDT, motivation was classified as either "amotivation" which is no motivation for action initiation, therefore constituting the extreme end of the continuum (no behavior). Or motivation is extrinsic leading to behavior that is self-determined to varying extent. Motivation may finally also be intrinsic which constitutes the other extreme end of the continuum at which behavior is entirely self-determined (see **Figure 1**). Therefore motivation determines whether behavior is executed. If behavior is initiated, the question remains, to which extent a person needs regulatory processes to be persistent in a behavior (regulatory styles) and to which extent a person feels autonomous to show the behavior, i.e., the PLOC.

Amotivation does not lead to any behavior and therefore no regulatory processes are required and the locus of control is perceived to be completely impersonal. Extrinsically motivated behavior is shown as a consequence of "external regulation," for example, when obeying a command. Behavior due to "introjected regulation" is initiated because it is expected by others or to avoid feelings of guilt or anxiety. In a BCI context this translates to healthy participants who feel obliged to spend their time on BCI experiments because they receive course credits or monetary compensation. "Identified regulation" depends on personal importance or even conscious valuing of a particular behavior; here, PLOC starts to adopt internal aspects (**Figure 1**). In a BCI context, identified regulation would refer to people who participate because it is personally important for them, but still it is not initiated self-determined, but due to external cues (advertisement for participation in the experiment). Finally, "integrated regulation" is characterized by regulatory processes that are congruent with the beliefs of this particular person and therefore represent this person's way of thinking and acting and behavior initiation is perceived as being an internal process (internal PLOC). The highest level of self-determination is reached when motivation and regulation both are intrinsic and behavior is initiated out of interest, enjoyment and inherent satisfaction with the task.

Empathy is another construct which may influence motivation. It was defined as an affective response resulting from the understanding of another person's emotional state and is similar to what the other person is believed to feel (Eisenberg and Fabes, 1991). It seems to be possible that healthy students who are interested in BCI experiments feel empathy for the potential BCI end-users, provided perspective taking (Eisenberg and Fabes, 1990). Perspective taking is a prerequisite for empathy (Spinrad et al., 2006). Feelings of empathetic concern with the goal to improve another person's situation can lead to motivation for pro-social behavior (Penner et al., 2005). In a BCI context, perspective taking could lead to participating in a BCI experiment as this supports BCI

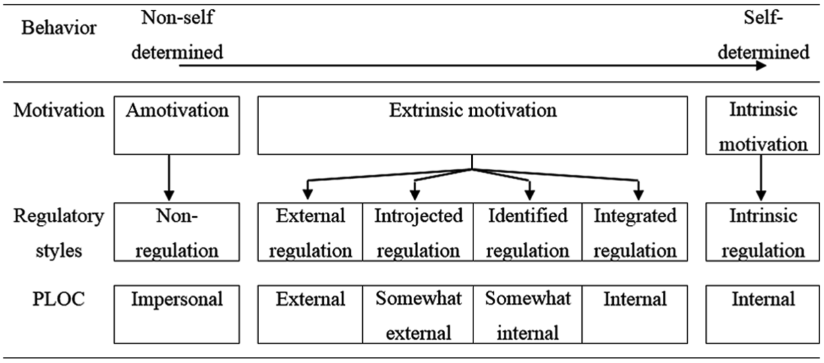

FIGURE 1 | The self-determination theory (slightly modified from Ryan and Deci, 2000). PLOC, perceived locus of control.

research which in turn benefits the end-user. Consequently, participation in a BCI experiment could be interpreted as pro-social behavior. We thus, speculated that empathy could support a shift toward integrated regulation and higher motivation.

On the basis of the SDT it seems further conceivable that there are participants for BCI studies with diverging motivation and regulatory styles. The aim of our study was to investigate whether people who initiate action as a result of integrated regulation would achieve better performance in a BCI task than those with introjected regulation. We defined performance as accuracy which corresponds to the percentage of correctly selected letters. We hypothesized (hypothesis H1) that we could strengthen or weaken participants' pre-existing helping motivation (high or low) by exposing them to a presentation about BCI research in a style that is congruent with initial motivation (very motivated = very informative and lively presentation vs. unmotivated = boring presentation). We also assessed mood because situational mood can change a person's momentary willingness for helping others (Carlson et al., 1988). We assumed (hypothesis H2) mood to be positively influenced by increasing motivation and negatively by decreasing motivation. We further predicted that highly motivated participants would be better able to focus their attention in a task that could possibly be of benefit for people with disabilities. This possible benefit might increase the value of the target stimulus thereby increasing the P300 amplitude (Johnson, 1986). We hypothesized that motivated participants would present higher P300 amplitudes as compared to less motivated participants (hypothesis H3). Finally, we previously speculated that in a more difficult task the effect of motivation would be more pronounced (Kleih et al., 2010). For this reason we not only decreased stimulus repetitions, but also increased task difficulty by introducing a memory task during spelling which required additional attention. We hypothesized (hypothesis H4) better BCI task performance (in terms of accuracy and speed) and a better performance in the memory task (hypothesis H5) in highly motivated as compared to less motivated participants.

MATERIALS AND METHODS

PARTICIPANTS

Participants were $N = 21$ healthy students from the University of Würzburg. We had to exclude one student because he answered socially desirable in all items taken from the SES-17 (Stöber, 1999; see Materials and Methods). The remaining sample consisted of $N = 20$ participants, of who $N = 14$ were female. The average age was $M = 23.35$ (SD = 3.87, range 18–35 years). None of the participants reported a history of neurological or psychiatric disorder. Participants were paid 8 Euro per hour and all were naïve with regards to BCI training. Participants gave informed consent for the study, which had been reviewed and approved by the Ethical Review Board of the Medical Faculty of the University of Würzburg, Germany.

MATERIALS

Advertisement for the study pronounced the purpose of developing assistive technology for severely ill people. A custom-made questionnaire was designed and inquired participants' motivation for participation and attitude toward BCI end-users (see **Table 1** for all statements). We assumed that participants who are more extrinsically motivated would report to be more interested in monetary reward (see, for example, items 6, 9, or 12) while participants who were also interested in the task and the BCI users would indicate strong interest and be not only extrinsically motivated (for example, items 4, 13, or 16). We assumed that primarily extrinsically motivated participants would be driven by what Ryan and Deci (2000) called introjected regulation while the also intrinsically motivated group would be more guided by integrated regulation. All statements were rated on a seven-point Likert scale (1 = I strongly disagree, 7 = I fully agree), negative items were inversed, and the sum of all items constituted the total score. Participants re-sent the questionnaire via e-mail and data were median split according to the total score.

To quantify motivation the Questionnaire for Current Motivation (QCM)-BCI and a visual analog scale (VAS) motivation were used. The QCM-BCI is an adapted version (Nijboer et al., 2008a) of the original QCM (Rheinberg et al., 2001). It comprises 18 items

Table 1 | Items of the custom-made questionnaire to separate highly motivated from less motivated participants.

Item no.	Item
1	I would enjoy doing a BCI task
2	I am eager to do my best
3	I believe I can handle the difficulty of the BCI task
4	I would not need a reward as I am very excited about how a BCI works
5	I would like to support and contribute to BCI research
6	I mainly participate in this study because of the monetary reward
7	I am scared that I could blame myself
8	I believe that everybody can control their brain activity
9	I was attracted to this study because of the promised payment
10	When I think about the BCI task I am a little nervous
11	Imagining people being able to communicate using BCIs is very exciting
12	If I did not participate in this study there would be negative consequences for me or I would feel guilty
13	I mainly volunteered for participation in this study because I would like to help people with paralysis
14	This study is a big challenge for me
15	I am knowledgeable in the field of BCI
16	BCI technology can be used to allow people with paralysis for communication. Therefore my main goal in participation is to contribute my share to facilitate these peoples' lives as their fate really touches me
17	I already used a BCI system
18	I am looking forward to participating

on four motivation components "mastery confidence," "incompetence fear," "challenge," and "interest" that have to be rated on a 7-point Likert scale. On the VAS motivation, participants had to indicate their motivation on a 10 cm long line ranging from 0 (not motivated at all) to 10 (extremely motivated).

We also included a questionnaire to measure empathy as it was hypothesized that people who are highly empathetic would score higher in helping motivation as they could better anticipate the needs of the BCI target population and take over more readily the patients' perspective. To assess empathy, the Saarbrücker Personality Questionnaire (SPF; Paulus, 2009) was used which is based on the Interpersonal Reactivity Index (IRI) by Davis (1983). It comprises 16 items to be rated on a 5-point Likert scale ranging from 1 ("does not describe me well") to 5 ("describes me very well"). Four subscales comprise four items each: "perspective taking" (PT), "fantasy" (FS), "empathic concern" (EC), and "personal distress" (PD). The Perspective taking subscale is a measure which indicates how well a person is able to take another person's point of view (e.g., "I try to look at everybody's side of a disagreement before I make a decision") while "fantasy" provides information about a person's ability to immerse into characters in movies or books (e.g., "I really get involved with the feelings of the characters in a novel"). The Empathetic Concern scale measures how much a person is concerned about another person's wellbeing (e.g., "I often have tender, concerned feelings for people less fortunate than me"). "Personal distress" measures whether a person feels tense or anxious when in close interaction with other people (e.g., "In emergency situations, I feel apprehensive and ill-at-ease"). While the subscales EC, FS, and PD are considered emotional factors of empathy, PT is considered a cognitive component (Paulus, 2009). Raw values of all four scales were transformed to T-norms.

Another measure used as an indicator for empathy was the "agreeableness" scale (e.g., "I sympathize with others' feelings") from the NEO-Five-Factor Inventory (NEO-FFI; Costa and McCrae, 1992; German version: Borkenau and Ostendorf, 1991). "Agreeableness" measures how important it is for a person to get along well with others and to be supportive of others. Items have to be answered on a 5-point Likert scale ranging from 1 ("strong disagreement") to 5 ("strong agreement").

The ability to concentrate, and thus, allocate attention on a task was measured with the *d2 test* (Brickenkamp, 1994). The amount of stimuli a person processes is an indicator of "speed," the amount of errors an indicator of "diligence." "Performance" included both, speed and diligence by subtracting the sum of all false responses from the amount of all processed stimuli.

As participants could be tempted to answer questionnaires which target empathy and agreeableness socially desirable, we included five items from the social desirability scale (Soziale Erwünschtheitsskala 17, SES-17; Stöber, 1999; e.g., "When in an argument I always stay factual and objective"). These items were integrated into the SPF questionnaire, but analyzed separately.

For the measurement of potential mood changes, we used the German version of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988; German version: Krohne et al., 1996). The PANAS is subdivided into a positive (PA) and a negative (NA) affect scale, each comprising 10 items which have to be answered on a scale ranging from 1 ("very slightly/not at all") to 5 ("extremely"). If participants agree more often to positive than negative items it is assumed that this person feels energetic, engaged, and focused while high scores on the negative scale indicate a state of distress and displeasing engagement with others.

To measure the amount of depressive symptoms as a further indicator of mood, we used the short version of the German version of the Center for Epidemiological Studies Depression Scale – CES-D (Allgemeine Depressionsskala = ADS, Hautzinger and Bailer, 1993). The ADS short version (ADS-K) comprises 15 items to be judged on a 4-point Likert scale ranging from 0 ("rarely or none of the time") to 3 ("most or all of the time") (for example, "I had trouble keeping my mind on what I was doing"). A score above 23 indicates clinically relevant symptoms of depression.

For assessment of memory and to increase task difficulty we used a slightly changed version of the Visueller und Verbaler Merkfähigkeitstest (= Visual and Verbal Memory Test = VVM; Schächtele and Schellig, 2009). The VVM is a test for the assessment of short- and long-term memory performance and therefore also an indicator of attention. Usually, participants have to memorize visual and verbal information in written form and are asked to reproduce what they had learned. We only used the verbal part which was presented acoustically by a native speaker because visual attention had to be focused on the letter matrix. The text "theater" was recorded with a TBone SC 400 microphone and after noise removal, saved as a.wav file which was later used for presentation. Participants had to listen to the 109 word text and were asked to remember as much information as possible while they were copy-spelling with the P300-BCI. We used this test as a measure of the ability to distribute cognitive resources between two tasks (BCI task and memory task). Memory was assessed twice: firstly in free recall participants had to note all the information they remembered and secondly, in cued recall they had to answer unambiguous questions about the text (e.g., "How many seats were in the theater?" or "How expensive was the theater?"). The VVM was evaluated according the test manual with correct responses being rated with up to two points per answer and a maximum of 24 points.

After finalization of the BCI task, participants received a custom-made post measurement questionnaire. We assessed, for example, interest in the BCI information presentation (e.g., "How interested were you in the BCI information session?") and whether participants were concentrated or felt exhausted by the BCI task (e.g., "Did you feel exhausted while using the BCI and listening to the memory task?," "Did you primarily focus on the BCI task or the memory task?" or "What else were you thinking about?").

STIMULI AND PROCEDURE

The motivated ($N = 9$; MG) and unmotivated group ($N = 11$, UG) were separated by median split (MD = 4.17) and did not differ concerning gender ($N = 3$ males in both groups) and age ($M_{\mathrm{MG}} = 23.22$, SD = 5.21; $M_{\mathrm{UG}} = 23.45$, SD = 2.56). Groups were invited for an information presentation about BCI scheduled 1 week before the BCI task. Prior to the presentation participants filled in questionnaires about demographic data, the

VAS, QCM-BCI, SPF (including the SES-17), and NEO-FFI agreeableness scale. Then both groups listened to one of two 25 min presentations. To further increase the motivation in the MG, the presentation was designed following instructional design criteria (Mayer, 2003; Reigeluth, 2009) by supporting text information with relevant other media such as pictures and videos which showed the BCI used by severely paralyzed end-users. The presenter spoke in conversational style and reported experiences with patients and stressed how important volunteers are for further development of BCI by giving examples and demonstrations of the interaction between the BCI expert and the end-user. The audience was invited to ask questions at any time. To decrease motivation in the UG, instructional design criteria were ignored and the presentation was restricted to black and white power point slides. Either no additional material such as pictures for illustration was offered or it was not congruent with the text information. No examples to clarify the content were provided and no videos were shown. Text was read from notes with a monotonous voice in ex-cathedra style. While the motivating presentation focused on the importance of BCI research for potential end-users, the demotivating presentation explained only the very basics of EEG recording such as what an electrode looks like and what material it is usually made of; the targeted end-users were mentioned only briefly.

After the presentation, attention was assessed with the d2 and motivation again with the VAS (see **Table 2**). An appointment for the BCI session was scheduled with every participant for the week after the presentation.

During the second appointment, the BCI session, participants were first asked to fill in the VAS, PANAS, QCM-BCI, and ADS-K (see **Table 2**). Then participants received an instruction on how to use the P300-BCI and a written information sheet in which the main contents of the presentation they had attended the week before were summarized to reactivate their motivational state before the P300-BCI spelling task.

Table 2 | Separation of participants into the motivated group (MG) and the unmotivated group (UG) and questionnaires that were assessed in both groups.

$N = 20$	
t1 group distribution one week prior to information session: custom-made questionnaire to split groups for the information presentation	
$N = 9$ motivated group (MG)	$N = 11$ unmotivated group (UG)
t2 prior to information session: VAS, QCM-BCI, SPF, SES-17, NEO-FFI agreeableness	
Motivating presentation	Demotivating presentation
t3 after information session: d2, VAS	
t4: prior to BCI task VAS, PANAS, QCM-BCI, ADS-K	
Calibration	
Copy-spelling 2 blocks, each comprising 4 runs (both words twice) VVM presentation: run 1 or 5	
t5: after BCI task VAS, QCM-BCI, PANAS, custom made post measurement questionnaire	

For the spelling task, participants were presented with a 6 × 6 matrix which contained the German alphabet and numerals 0–9. Participants first completed two copy-spelling (Kübler et al., 2001) calibration runs in which the words "BRAIN" and "POWER" had to be spelled to derive classification coefficients for the following eight experimental copy-spelling runs. The word-to-copy appeared above the matrix and next to it the letter to be copied (target character) in parenthesis. The participants' task was to pay attention to the target character and to silently count the number of times it was intensified. For each target character three sequences of flashes (one trial) were presented. As the number of sequences was low, no dynamic stopping method (Schreuder et al., 2013) was applied. Each flash lasted 31.25 ms followed by an inter-stimulus interval of 350 ms. After one trial the matrix stopped flashing for 5 s in which the participant had time to locate the next target character to be spelled. After calibration, participants performed two blocks of copy-spelling, each comprising four runs. In one run five characters had to be spelled ("BLUME" or "RADIO"). Thus, in each block both words had to be spelled twice. In none of the copy-spelling runs feedback was provided to avoid motivating the participants by correctly selected letters. The auditory VVM memory task was presented to the participants with a Sony MDR-15 headphone. Presentation of the memory task was counterbalanced across all subjects to control for fatigue. The text to memorize was thus, presented either during run 1 or during run 5. While cued recall was required directly after the presentation, free recall was obtained 20 min later either after run 4 or after run 8, respectively. After spelling, participants again filled in the VAS, PANAS, QCM-BCI, and the custom-made post-measurement questionnaire. Therefore, all motivation and mood questionnaires were assessed three times with exception of the VAS motivation and mood which were assessed four times (see **Table 2**). All participants were offered the opportunity to spell one or two additional words in the free-spelling mode of the system.

DATA ACQUISITION AND CLASSIFICATION

EEG data collection was controlled by the BCI2000 (Schalk et al., 2004). The electroencephalography (EEG) was measured with an electrode cap (easy cap) with 12 Ag/AgCl electrodes located at positions F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, PO7, PO8, and Oz following the international 10–20 standard system (Sharbrough et al., 1991) referenced to the right and grounded to the left mastoid. Four electrooculography (EOG) electrodes were placed at the temples on a point between the hairline and the eye (left and right, horizontal EOG) and above and below the left eye in line with the pupil when looking straight (vertical EOG). Data was filtered online with a high pass of 0.1 Hz, a low pass of 30 Hz and a notch filter at 50 Hz. The EEG signal was amplified using a g.USBamp (Guger Technologies, Austria). Impedance was kept below 5 kΩ and the sampling rate was 256 Hz. Data were processed and stored on a laptop. For data classification online and offline stepwise linear discriminant analysis (SWLDA) was applied. SWLDA separates the data into two classes (target and non-target signals) both obtaining equal covariance matrices. It calculates a linear equation which depends on the spatiotemporal features of the signals and separates the data classes. This maximizes the distance between the means of the two classes while also minimizing the variance within one class (Lotte et al., 2007). Input features that predict the target label statistically significant are added to the linear equation to explain the largest amount of unique variance while those which are no longer significant are removed. Further details on SWLDA are described, for example, in Krusienski et al. (2008).

DATA ANALYSIS

For all questionnaire data, scores were transformed into the according norms for further statistical analysis. The EEG data were corrected for artifacts (>50 μV) and baseline (-100 to 0 ms). The P300 was defined as the maximum positive peak occurring between 200 and 600 ms after stimulus onset and was chosen by semiautomatic global peak detection of Brain Vision Analyzer 2® (Brain Products, Germany). Targets and non-targets were averaged and grand averages were compared for the two motivation groups. Spelling speed was measured as the number of sequences needed offline to achieve 70% accuracy. For statistical analysis, cases were weighted as the number of participants was unequal in the two groups. We used IBM SPSS 20® as analysis software. Dependent variables were mood, empathy scores, P300 amplitudes, and BCI performance (online accuracy), spelling speed and performance in the memory task. The level of significance was set to $\alpha = 0.05$.

RESULTS

If not indicated otherwise, we used repeated measures ANOVA with time of measurement as within subjects' factor and group (MG and UG) as between-subjects factor. Time of measurement either comprised three levels, before the information presentation, and before and after the BCI session or four levels (VAS scales); before and after the information session and before and after the BCI session.

MOTIVATION

To investigate the effect of motivation manipulation and motivation during the BCI task, we used the VAS motivation and the QCM-BCI. For the VAS we found a main effect of *group* for overall motivation [$F_{(1,18)} = 5.34$, $p < 0.05$]. The MG ($M = 7.84$, SD = 1.81) was significantly more motivated than the UG ($M = 6.43$, SD = 1.35) confirming successful grouping and sustained higher motivation in MG as compared to UG [$F_{(1,18)} = 5.34$, $p < 0.05$]. For the QCM-BCI we found a significant main effect of *group* for *interest* with the motivated group being significantly more interested ($M = 5.12$, SD = 1.04) than the unmotivated group [$M = 4.13$, SD = 0.72; $F_{(2,36)} = 8.98$, $p < 0.01$], which again confirmed successful grouping. We did not find a main effect of time. Thus, we reject H1 which stated that the motivational state (motivated vs. unmotivated) prior to the information session could be further intensified by our manipulation procedure.

MOOD

To investigate the effect of motivation manipulation on mood and mood during the BCI task we used the VAS mood and the PANAS. To control for a possible bias caused by pre-existing depressive symptoms, we used the ADS-K. The VAS mood yielded a significant main effect of *group* [$F_{(1,18)} = 15.08$, $p < 0.01$] with MG being in significantly better mood ($M = 7.71$, SD = 1.19) compared to UG ($M = 6.19$, SD = 1.37). In the PANAS a significant main effect of *time* was found [$F_{(1,18)} = 21.28$, $p < 0.001$] with higher negative affect scores before the BCI measurement ($M = 14.05$, SD = 2.93) as compared to thereafter ($M = 11.30$, SD = 1.96). Concerning the ADS-K scores no signs of depression and no group differences were found. All other effects were not significant.

Therefore, H2 of better mood when being motivated was only partially supported by the data because the motivated group was in better mood as indicated by VAS, but this difference existed from the beginning independent of motivation manipulation. The decrease of negative affect was independent of group.

EMPATHY

Regarding empathy we used multivariate analysis of variance (MANOVA) with the SPF subscale values and the NEO-FFI agreeableness scale. No significant results were found.

ATTENTION AND P300 AMPLITUDES

As an indicator of attention we used the d2 scores and the P300 amplitudes in the BCI task. Two participants of the MG did not understand the d2 instruction and therefore crossed out the wrong letters throughout the whole test. Thus, for d2 analyses only data of $N = 18$ participants were available. H3 stated that highly motivated participants would better allocate attention leading to higher P300 amplitude and better performance. MANOVA with d2 subscales as dependent variables, revealed significantly higher *concentration performance* in the UG [$F_{(1,16)} = 10.10$, $p < 0.01$, $M_{\mathrm{UG}} = 93.36$ $\mathrm{SD}_{\mathrm{UG}} = 5.68$ vs. $M_{\mathrm{MG}} = 71.00$, $\mathrm{SD}_{\mathrm{MG}} = 22.46$]. There was a trend for the UG to be more *diligent* [$F_{(1,16)} = 4.50$, $p = 0.05$, $M_{\mathrm{UG}} = 72.00$ $\mathrm{SD}_{\mathrm{UG}} = 25.74$ vs. $M_{\mathrm{MG}} = 42.86$ $\mathrm{SD}_{\mathrm{MG}} = 32.40$]. *Speed* did not differ between groups.

P300 amplitudes at Pz were on average $M = 7.32$ μV (SD = 2.53) in the MG and $M = 7.10$ μV (SD = 1.78) in the UG. When entering electrode position (Fz, P3, Pz, P4, C3, Cz, C4) as within-subjects variable in the repeated measures ANOVA a significant main effect for *electrode* [$F_{(2.41,43.31)} = 15.39$, $p < 0.001$, after Mauchly's test of sphericity was significant $\chi^2_{(20)} = 64.31$, $p < 0.001$, Greenhouse–Geisser corrected ($\varepsilon = 0.49$)] but no effect of *group* was found.

Therefore, H3 of better attention allocation as indicated by higher d2 test performance and higher P300 amplitudes in the MG had to be rejected. Contradictory to H3 we found that the UG concentrated better and was more diligent (trend) than the MG.

PERFORMANCE AND SPELLING SPEED

H4 postulated better BCI performance measured as online accuracy and faster spelling speed measured as sequences needed for correctly spelling 70% accuracy with one, two, and three sequences in the MG compared to the UG. Overall, participants achieved an average online accuracy of $M = 97.15\%$ (SD = 2.78). The MG reached an accuracy of $M = 97.00\%$ (SD = 2.68) and the UG an accuracy of $M = 97.27\%$ (SD = 2.99). The average single trial accuracy (offline) reached 76% or above in both groups. A 4 × 2 repeated measures ANOVA with *sequences* (after one, two, three sequences offline, and overall online) as within-subjects factor and group as between-subjects revealed a main effect of *sequences* [$F_{(1.99,35.86)} = 34.69, p < 0.00$, Greenhouse–Geisser corrected ($\varepsilon = 0.79$) after Mauchly's test for sphericity was significant $\chi^2{}_{(5)} = 29.24$, $p < 0.05$]. Within-subjects contrasts were in the expected direction ($1 < 2 < 3$). No significant differences between groups were found. Thus, H4 of higher performance and spelling speed in the MG had to be rejected.

SHORT-TERM MEMORY AS AN INDICATOR OF ATTENTION

The fifth hypothesis stated that we could increase task difficulty by adding a memory task to the copy-spelling task and that motivated participants were better in the VVM task and would therefore remember more facts from the memory test in the direct recall and the free recall after 20 min. However, the additional memory task was probably too difficult for participants as most did not reach average T-norm values of between 40 and 60 but ranked much below (overall $M = 18.15$, SD = 14.09 for the cued recall and $M = 24.05$, SD = 11.15 for the free recall). To investigate group differences, we compared the MG and UG and found a significant main effect for *time* [$F_{(1,18)} = 4.58$, $p < 0.05$] but no effect of *group*. Surprisingly, within-subjects contrasts revealed significantly higher memory performance in the free as compared to the cued recall [$F_{(1,18)} = 8.80$, $p < 0.01$]. However, H5 of better memory performance in the MG could not be confirmed by the data.

FREE SPELLING

To assess another behavioral indicator of motivation, participants were asked after finishing copy-spelling whether they wished to try free-spelling with a self-chosen word. Nineteen participants accepted the offer and only one participant who belonged to the unmotivated group refused to try free-spelling. The freely chosen words were between three and six characters long and there was no group difference with regards to time spent with free-spelling [$t_{(18)} = 0.90$, $p = 0.11$].

POST-MEASUREMENT QUESTIONNAIRE

Results of the post-measurement questionnaire revealed that from the MG $N = 7$ participants reported the information presentation to be very interesting while only $N = 3$ from the unmotivated group did so. In the UG most participants judged the information presentation as completely uninteresting ($N = 6$). Thus, on the descriptive level we can state that the information presentations were indeed perceived qualitatively different.

Furthermore, $N = 5$ from the MG and $N = 8$ from the UG reported that they subjectively did not judge the BCI task as exhausting. When being asked whether participants were primarily focused on the BCI spelling or the VVM auditory task, $N = 3$ from MG and $N = 8$ from UG reported to have focused primarily on the BCI spelling task. All participants in the MG but only $N = 3$ in the UG reported that they were concentrated during the task.

POST HOC ANALYSIS FOR EMPATHY

The values in the SPF subscale perspective taking were considered to be highly important in this paradigm as we aimed at specifically increasing "motivation for helping." Therefore we regrouped the sample by the median of their SPF PT values. All participants who had values of 46.27 (Md) or less ($N = 10$) were grouped into the "less able to take others' perspective" group (LAPT), all participants who had values above 46.27 ($N = 10$) were grouped into the "highly able to take others' perspective" group (HAPT). In the HAPT group there were $N = 4$ participants of the original high motivation group and $N = 6$ participants of the original unmotivated group. There were $N = 4$ male participants in this group and mean age was 23.52 (SD = 4.79). In the LAPT group there were therefore $N = 5$ participants of the original high motivation group and $N = 5$ participants of the low motivation group. Two participants were male and mean age was 23.15 (SD = 3.21).

We post hoc applied the hypotheses H1–H5 to the LAPT vs. HAPT groups.

Motivation, mood, empathy

For all dependent variables the same analyses were performed as described above. Motivation (VAS, QCM-BCI) and mood (VAS, PANAS, ADS-K) did not differ between the groups.

Regarding empathy, we used MANOVA with the SPF subscale values (other than PT) and the NEO-FFI agreeableness scale as dependent variables and group as between-subjects variable. The HAPT group showed significantly higher *Empathetic Concern* [$F_{(1,18)} = 5.48$, $p < 0.05$] and a trend toward lower *Personal Distress* [$F_{(1,18)} = 3.43$, $p = 0.08$].

Attention and P300 amplitude

The ability to concentrate (d2 scores) did not differ between groups. Thus, H3 of higher capability to focus attention in the HAPT had to be rejected.

The comparison of P300 amplitudes with the within-subjects factor *electrode* (Fz, C3, Cz, C4, P3, Pz, P4) and the between-subjects factor *group* yielded main effects for *electrode* [$F_{(6,108)} = 13.50$, $p < 0.001$] and *group* [$F_{(1,18)} = 6.64$, $p < 0.05$]. Post hoc tests revealed a significantly higher P300 amplitude at P3 (mean difference = 2.03, $p < 0.05$, $M_{\mathrm{LAPT}} = 5.64$, SD = 2.29, $M_{\mathrm{HAPT}} = 3.73$, SD = 0.96), Pz (mean difference = 2.14, $p < 0.05$, $M_{\mathrm{LAPT}} = 6.90$, SD = 2.48, $M_{\mathrm{HAPT}} = 4.87$, SD = 1.59) and P4 (mean difference = 1.94, $p < 0.05$, $M_{\mathrm{LAPT}} = 5.83$, SD = 2.04, $M_{\mathrm{HAPT}} = 4.02$, SD = 0.88) in the LAPT as compared to the HAPT group (see **Figure 2**). Contradictory to H3 of higher P300 amplitudes in the HAPT, we found higher P300 amplitudes in the LAPT group.

Performance and spelling speed

Again a 4 × 2 repeated measures ANOVA with *sequences* (after one, two, three sequences, and overall online) as within-subjects factor and *group* as between-subjects factor revealed a main effect of *sequences* [$F_{(2.02,36.43)} = 38.38$, $p < 0.000$, Greenhouse–Geisser corrected ($\varepsilon = 0.68$) after Mauchly's test for sphericity was significant $\chi^2{}_{(5)} = 26.86$, $p < 0.05$]. Within-subjects contrasts

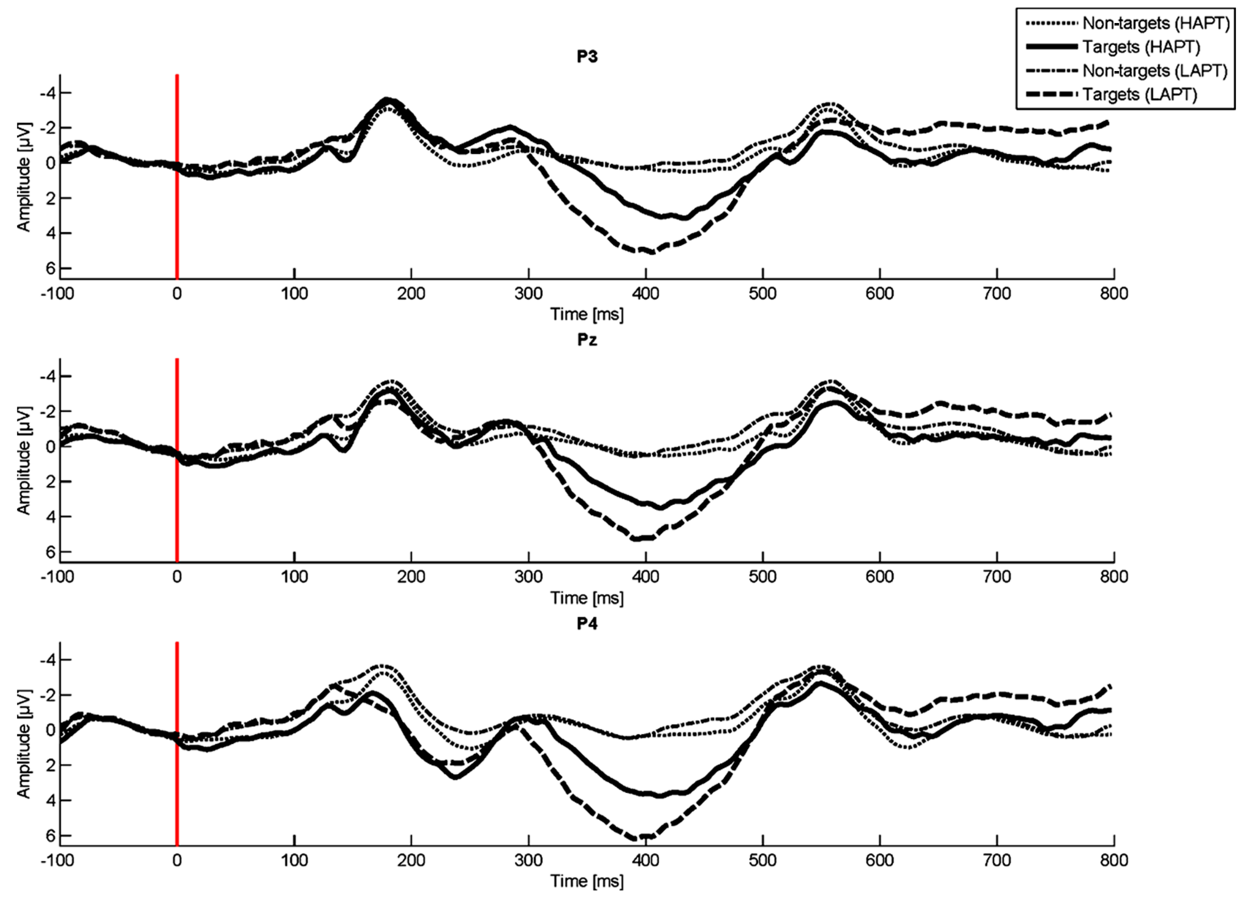

FIGURE 2 | P300 amplitudes at P3, Pz, and P4 for the low (LAPT) and the high (HAPT) *perspective taking* group.

were in the expected direction ($1 < 2 < 3$). For overall online performances, no significant differences between groups were found ($M_{\text{LAPT}} = 98.60$, SD = 1.63; $M_{\text{HAPT}} = 95.94$, SD = 2.98). Thus, H4 of higher performance and spelling speed in the HAPT as compared to the LAPT group had to be rejected.

DISCUSSION

In this study we investigated the effect of motivation for helping and perspective taking on BCI performance. We successfully sorted participants in a motivated and unmotivated group, but were not able to increase and decrease the initial motivation by means of a motivation congruent presentation. With our advertisement it seems likely that only participants who were interested in the topic were attracted to learn about the functionality of how a BCI works. Additionally, just the fact that participants received information in the BCI information presentation, irrespective of the patient-related content, might have increased their involvement in the BCI task. Maybe confronting participants with a situation in which empathy could have led to an action directly would have been more successful. Batson et al. (1983) administered mild electrical shocks to a test person who had to perform digit-recall. Observers of this situation indicated high empathy and willingness to help the test person. Dovidio et al. (1990) presented their participants with a video of a student who had been ill and thus could not fulfill all requirements in time for entering graduate school. Participants indicated commitment to support this person actively. In such scenarios, motivation for helping had a clear action direction which probably facilitated action initiation. As we could not confront our subjects with a real BCI end-user, our manipulation may have been less powerful. Furthermore, the time between the presentation and the BCI experiment may have caused possible effects to extenuate. Our motivation manipulation which was supposed to strengthen pre-existing motivation was quantitatively unsuccessful as motivation of the MG could not be increased and that of the UG not decreased; however, qualitatively it was perceived as intended. The initial motivation had no effect on any of our dependent variables and thus, we had to reject H1.

Our second hypothesis stated that we could increase mood together with motivation. As our motivation manipulation failed, we also had to reject H2 even though we found better mood in the highly motivated group. The more negative affect participants experienced before the BCI task as compared to thereafter, was independent of group and therefore may be attributed more to the test situation instead of the motivation manipulation.

Our results were also contradicting our hypothesis H3 which stated that subjects of the MG should present with higher P300 amplitudes due to better allocation of attention. Thus, we could not confirm Kleih et al. (2010) who found higher P300 amplitudes in highly motivated as compared to less motivated participants. Attention allocation as measured with the d2 was higher in the UG as compared to the MG. A possible explanation is that participants in the motivated group were very attentive throughout the presentation and thus, had fewer resources for attention allocation in the d2 test. Similarly, after group re-distribution, participants who were less able to take perspective, i.e., were less empathetic (LAPT group), presented with higher P300 amplitudes. Both results are in line with Johnson's model which postulates that allocation of attentional resources affects the P300 amplitude (Johnson, 1986). The resources of the motivated and the highly empathetic group might have been limited. Avenanti et al. (2005) showed that empathetic involvement affects brain responses. Their participants watched needles being penetrated through a body model and in consequence participants' motor evoked potentials (MEPs) as measured with transcranial magnetic stimulation (TMS) decreased in amplitude in sensorimotor regions corresponding to the penetrated body parts. The authors assumed that empathetic involvement led to emotional arousal which had an inhibitory effect on the MEP response. Although we did not measure emotional arousal it might well be that the more subjects were involved in the purpose of BCI the stronger the negative effect on the P300 amplitude. The Yerkes and Dodson (1908) law which postulated an inverted U-shaped relation between task performance and arousal may explain this result. It is important to note that in this study we refer to arousal as a state of emotional involvement and not to general cortical excitability which is also a definition of arousal (Polich and Kok, 1995; Polich, 2007).

Eisenberg and Eggum (2009) explain lower attention capacity in the context of empathy by the lack of self-regulation. They state that in case empathy is not characterized by compassionate concern about a person's wellbeing but by personal distress, attentional resources are negatively affected and lead to a self-focus. The primary goal of a person would be to alleviate one's own negative state. In our BCI context, this translates to higher arousal in the highly empathetic group because bearing in mind the health state of possible BCI end-users could have caused personal distress and lower attentional resources for the BCI task. Furthermore, in case self-regulatory processes are required to cope with emotional involvement, also less pro-social behavior is observed (Eisenberg and Fabes, 1990; Penner et al., 2005) as the focus of the person is self-centered. Therefore, participants in our study probably did not take extra effort to concentrate specifically hard on the VVM task as they were focusing on reduction of possible negative emotions.

BCI performance could not be positively influenced, neither by motivation, nor by empathy which rejects our hypothesis H4 as well as previous work by Kleih and Kübler (in press) who found a correlation between mastery confidence and the number of sequences needed to spell with 70% accuracy. However, Kleih and Kübler (in press) investigated a sample of ALS patients who were highly intrinsically motivated and also showed a ceiling effect of performance. This patient sample is not comparable to healthy students who know that for themselves a BCI is not required for communication purposes and for who integrated regulation, i.e., acting in congruence with one's own beliefs is probably the highest motivation level to reach (Ryan and Deci, 2000).

In the memory task measured with the VVM no significant differences between the motivated and unmotivated groups nor the HAPT and the LAPT groups were found so we had to reject our fifth hypothesis H5. This might be explained by the task difficulty. As it turned out, the memory task was basically ignored by participants. Accuracies were constantly high in the BCI task, even though only three sequences were used while the T-norm scores for the VVM were far below the normal average. This indicates that participants allocated attentional resources on the BCI task only, while ignoring the auditory memory task. As Carr (2004) explained, for every incoming stimulus, it needs to be decided whether this stimulus should be processed early (= superficially) or deeply (= determination of stimulus identification, meaning, and preparation for possible response; Carr, 2004). In this VVM task, the auditory stimuli were probably not processed deeply as attention was focused on the primary area of stimulus presentation on the computer screen. Consequently no bimodal processing occurred. This phenomenon of impaired processing of auditory stimuli when being presented together with visual stimuli is known as Colavita visual dominance effect (Colavita, 1974). The Colavita effect was repeatedly reported (Laurienti et al., 2004; Molholm et al., 2004; Spence, 2007, 2009) and was found not to be simply dependent on the intensity or probability of the presented stimuli (Spence et al., 2012). Koppen and Spence (2007) explained the Colavita effect with endogenous attention allocation toward visual perception to compensate for its low alerting properties in comparison to the auditory domain which immediately causes an orientation reaction (Talsma et al., 2007; Spence et al., 2012). Indeed it was shown that manipulation of endogenous attention by, e.g., decreasing the likelihood for the visual stimulus decreased also the Colavita effect (Egeth and Sager, 1977).

With regards to the SDT (Ryan and Deci, 2000), it remains unclear, whether participants applied *introjected* (avoidance of feelings of guilt) or *integrated* regulation. But it might be that participants in the HAPT group were too much involved in the task and their *identified regulation* hindered them to focus on the BCI task. The LAPT group which was more emotionally distant did not show this detrimental effect on P300 amplitude.

In conclusion, we could not increase or decrease state motivation by emphasizing the user-centered aspect of BCI research. Contrary to previous studies, motivation did not affect P300-BCI performance. Subjects with lower trait empathy, who were likely to be less emotionally involved, and thus, better able to focus attention on the task, presented larger P300 amplitudes than those with higher trait empathy. Therefore, we conclude that there is a moderate influence of empathy on the P300 within a BCI paradigm. Further research on empathy and motivation in BCI is required.

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Control beliefs can predict the ability to up-regulate sensorimotor rhythm during neurofeedback training

Matthias Witte[1], Silvia Erika Kober[1], Manuel Ninaus[1], Christa Neuper[1,2] and Guilherme Wood[1]*

[1] Department of Psychology, University of Graz, Graz, Austria
[2] Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, Graz, Austria

Edited by:
Reinhold Scherer, Graz University of Technology, Austria

Reviewed by:
Juliana Yordanova, Institute of Neurobiology, Bulgarian Academy of Sciences, Bulgaria
Stefano Silvoni, I.R.C.C.S. S.Camillo Hospital Foundation, Italy
Moritz Grosse-Wentrup, Max Planck Institute for Biological Cybernetics, Germany

Correspondence:
Guilherme Wood, Department of Psychology, University of Graz, Universitaetsplatz 2/III, 8010 Graz, Austria
e-mail: guilherme.wood@uni-graz.at

Technological progress in computer science and neuroimaging has resulted in many approaches that aim to detect brain states and translate them to an external output. Studies from the field of brain-computer interfaces (BCI) and neurofeedback (NF) have validated the coupling between brain signals and computer devices; however a cognitive model of the processes involved remains elusive. Psychological parameters usually play a moderate role in predicting the performance of BCI and NF users. The concept of a locus of control, i.e., whether one's own action is determined by internal or external causes, may help to unravel inter-individual performance capacities. Here, we present data from 20 healthy participants who performed a feedback task based on EEG recordings of the sensorimotor rhythm (SMR). One group of 10 participants underwent 10 training sessions where the amplitude of the SMR was coupled to a vertical feedback bar. The other group of ten participants participated in the same task but relied on sham feedback. Our analysis revealed that a locus of control score focusing on control beliefs with regard to technology negatively correlated with the power of SMR. These preliminary results suggest that participants whose confidence in control over technical devices is high might consume additional cognitive resources. This higher effort in turn may interfere with brain states of relaxation as reflected in the SMR. As a consequence, one way to improve control over brain signals in NF paradigms may be to explicitly instruct users not to force mastery but instead to aim at a state of effortless relaxation.

Keywords: EEG, locus of control, neurofeedback, performance prediction, sensorimotor rhythm

INTRODUCTION

In the last twenty years of neuroimaging research a clear view has emerged that patterns of brain activity can be directly linked to different cognitive states. Users of neurofeedback (NF) can learn to modulate their brain signals over several training sessions. Alternatively, using multivariate analysis methods one can try to decode these brain states and use the output of a classifier to control external devices in a so-called brain-computer interface (BCI). A key concept behind all these approaches is the assumption that the brain activations associated with a cognitive state are stable over time, highly specific and distinct from other states. However, these prerequisites are not always fulfilled and the neural correlates of a cognitive state are masked by various sources of physiological and environmental noise. The search for reliable predictors of performance therefore remains one of the major challenges in this field of research.

To achieve a reliable readout of brain patterns most BCI studies have put the primary load on the machine-learning side. This seems a straightforward approach as the goal of many BCIs is to detect overt brain states, like decoding movement parameters or stimulus-evoked activity (for review see: Donoghue, 2008; Green and Kalaska, 2011). Here, a standard procedure is to adapt the classification across participants and sessions (McFarland et al., 2005; Shenoy et al., 2006; Blumberg et al., 2007; Vidaurre et al., 2007). In contrast, NF is inspired by conditioning and often modulates a covert, unconscious state by immediate reward. One of the best described examples is the voluntary regulation of slow cortical potentials in healthy participants and paralyzed patients (Birbaumer et al., 1999; Kubler et al., 1999, 2001; Neumann and Birbaumer, 2003). It has been shown that self-regulation of these brain signals is optimally learned without giving definite strategies (Birbaumer et al., 1988; Neumann et al., 2003). An issue in this design is that users may feel lost at early stages of training and start to explore different ways to regulate their brain activity. Due to the immediate closed-loop feedback this "trial-and-error" learning can result in progressively better control and is believed to ultimately lead to an automated skill (Wolpaw and McFarland, 1994; Neumann and Birbaumer, 2003; Hinterberger et al., 2005). However, the literature has also described a significant proportion of people who are unable to gain control over signals in BCI and NF paradigms (Guger et al., 2003; Kübler et al., 2004; Nijboer et al., 2008; Blankertz et al., 2010b). The reasons for this phenomenon of "illiteracy" are still unknown and only few studies tried to assess predictors of successful performance. Factors like mood, motivation, intelligence and personal traits have been reported to show only moderate correlations to performance in healthy and impaired participants (Nijboer et al., 2008, 2010; Kleih et al., 2010; Hammer et al., 2012). Yet there is evidence from neuropsychological tests that part of the variations seen in NF training may be connected to memory and attentional abilities of participants (Roberts et al., 1989; Daum et al., 1993; Holzapfel et al., 1998). In particular, fronto-parietal gamma-band activity has been reported to influence sensorimotor activity, presumably reflecting attentional networks (Grosse-Wentrup and Schölkopf, 2012). Furthermore, the initial performance level was shown to have some predictive value for future performance (Neumann and Birbaumer, 2003; Kübler et al., 2004). These results may thus suggest that the overall, not necessarily task-related, cognitive resources impact the level of control in NF and BCI tasks.

Given that all experiments in the field of BCI and NF imply the use and interaction with technologic environments it is surprising that only one study directly assessed how technology commitment may impact performance (Burde and Blankertz, 2006). The authors evaluated the "locus of control of reinforcement" (LOC), a psychological construct developed by Rotter's social learning theory (Rotter, 1966). According to this theory, people with an external LOC tend to attribute the result of their own actions to external sources like luck, chance or unpredictable circumstances. Conversely, an internal LOC describes the personal trait to link results and own actions and thus people feel that they are in control of the situation. Burde and Blankertz (2006) assessed the general control belief with an IPC (Internal, Powerful Others and Chance) questionnaire (Krampen, 1981) and the specific interaction with technology as indexed by the KUT (Kontrolluеberzeugug im Umgang mit Technik), i.e., control beliefs while dealing with technology (Beier, 1999, 2004). They reported a positive correlation between KUT scores and BCI performance in 12 healthy participants partaking in a motor imagery task. However, only a single session was recorded and the features for classification were individually adapted for each participant.

We therefore sought to clarify whether control beliefs while dealing with technology, as reflected in the KUT score, can predict performance in NF training over several sessions. To this end, 10 participants trained to gain control over their sensorimotor rhythm (SMR, 12–15 Hz) in 10 sessions spanning up to five weeks via real-time visual feedback. An additional control group of 10 participants took part in the same protocol but received sham visual feedback. SMR is known to originate from thalamo-cortical loops and increased SMR amplitude is found during states of relaxed wakefulness with reduced sensory and motor excitability (Gruzelier et al., 2006; Serruya and Kahana, 2008). Because SMR desynchronizes during movement execution and during motor imagery in an event-related manner (Pfurtscheller and Neuper, 1997; Pfurtscheller and Lopes Da Silva, 1999; McFarland et al., 2000), it has been extensively used in BCI research (Cincotti et al., 2003; Pfurtscheller et al., 2006; Mellinger et al., 2007; Blankertz et al., 2010a). The opposing effect of voluntarily increasing SMR amplitude can also be learned through NF training (Vernon et al., 2003; Egner et al., 2004; Hoedlmoser et al., 2008; Weber et al., 2011; de Zambotti et al., 2012). However, only few studies investigated the changes of SMR over longer time periods of training and, to our knowledge, there is no report on the influence of technology commitment in training scenarios.

MATERIALS AND METHODS

PARTICIPANTS

Twenty healthy participants (10 males, mean ± SD age: 24.4 ± 1.8 years) participated in this study after giving written informed consent. The study was approved by the local ethical committee of the University of Graz in accordance to the Declaration of Helsinki. No participant had any experience in NF- and BCI-paradigms prior to this study. In a double-blinded approach participants were randomly assigned to one group of 10 participants: either receiving real visual feedback coupled to brain rhythms experimental group (EG) or receiving a video of sham feedback randomly taken from one of these real feedback sessions control group (CG).

EXPERIMENTAL PARADIGM

We recorded brain signals with a 16 Ag/AgCl electrode system (g.USBamp, g.tec medical engineering GmbH, Austria) mounted according to the International 10–20 EEG system and referenced to the left mastoid. Ground electrode was set on Fpz electrode and signals digitized at a sampling frequency of 256 Hz. In addition, electrooculography (EOG) was recorded to eliminate eye movement artifacts post-hoc.

Online visual NF was implemented via SIMULINK software (The MathWorks, Natick, USA). Raw signals were band-pass filtered in the respective target bands (precise frequencies see below; 6th order butterworth IIR) and squared to obtain power estimates. To ensure a smooth visual feedback we then applied a moving average of 256 samples and updated the computer screen at a rate of 10 Hz. The feedback design was adopted from a previous study (Weber et al., 2011): while a central bar was coupled to the user's absolute power of the SMR (12–15 Hz) recorded at electrode Cz, two smaller flanking bars reflected absolute power in θ (4–7 Hz) and β (21–35 Hz) ranges at Cz, respectively. This setup of three moving bars was chosen to ensure voluntary regulation of SMR and at the same time minimize influence of eye movements (θ), muscle activations and other task-unrelated components (β). Each of the 10 sessions started with a first baseline run (3 min) where participants were instructed to relax and watch the moving feedback bars coupled to their brain activity without trying to control them. Then six feedback runs (3 min each) were recorded and participants tried to gain voluntary control over their brain rhythms, i.e., an increase of power was associated with an increase of the feedback bar.

Participants' task was to increase the height of the central bar and at the same time keep the two smaller bars as low as possible. To facilitate the recognition of current performance, participants received an additional rewarding feedback whenever the bigger central bar reached a pre-defined threshold without concomitant artifacts: a number in the middle of the bar served as reward counter and was incremented by one unit each time this target state was achieved for 250 ms (i.e., between 0 and 720 points could be earned per run). The individual threshold was initially determined on the median absolute SMR power of the baseline run and progressively adapted using the median power of each previous feedback run. Similarly, the small flanker bars were calibrated once on the baseline recording of each day (threshold: mean power + 1 SD) and feedback bars changed color from green to red whenever influence of artifacts reached the individual thresholds.

DATA ANALYSIS

All preprocessing and data analysis of EEG recordings were performed offline using the Brain Vision Analyzer software (version 2.01, Brain Products GmbH, Munich, Germany). First, 1 s epochs of data were inspected for eye movement artifacts by a trained investigator and contaminated epochs were manually rejected. Next, we applied an automated rejection of additional artifacts like muscular activity, high-frequency noise or drifts (rejection criteria: step >50.00 μV per sampling point, absolute voltage value >120.00 μV).

In line with past studies (Weber et al., 2011; de Zambotti et al., 2012), absolute values of SMR power in a fixed range (12–15 Hz) were calculated for all epochs of length 1 s using Brain Vision Analyzer's built-in method of complex demodulation. For each run, this procedure outputs mean SMR power over the whole time window of 3 min.

LOCUS OF CONTROL OF REINFORCEMENT

The LOC was assessed in the context of dealing with technology by the KUT questionnaire (Beier, 1999, 2004). This one dimensional construct of LOC is a subjective 5-point Likert scale rating that considers actual technologic biography in eight items (range of total score: 8–40). The questionnaire is available in German and has a high reliability. To monitor control beliefs over time each participant was asked twice, before the first and after the 10th training session.

STATISTICAL DATA ANALYSIS

Absolute SMR power values were calculated for each run separately and mean power was tested for differences using a 2 × 3 × 2 repeated measures ANOVA with between-factor group (EG vs. CG) and within-factors session (sessions 1–3, sessions 4–7, sessions 8–10) and run (runs 2–4, runs 5–7). Measures of effect size were reflected in partial eta-squared (η^2) and observed power (Obs_{pow}). Post-hoc tests, if necessary, were run on significant effects using Fisher's Least Significant Difference (LSD) test.

To report trends of power changes we used a linear fit and assessed the significance of the regression slope using t-statistics of the regression model implemented in MATLAB (The MathWorks, Natick, USA). Group-wise comparisons of power and KUT values were assessed using paired t-test. All statistics considered a nominal probability level of $p < 0.05$ significant.

RESULTS

CONTROL BELIEFS AND NEUROFEEDBACK TRAINING

As a first step, we quantified the distribution and changes of our predictor variable across the population of participants. Our assessment of control beliefs while dealing with technology before NF training revealed no differences ($t(18) = -0.15, p = 0.88$ n.s., paired t-test) in KUT scores between the EG using real NF and the CG that relied on sham feedback. Overall scores were rather high varying only little around a value of 33 on average. Next, we intended to characterize differences within the groups in more detail. When dividing each group into subgroups using median-split, significant differences of 7.42 and 7.2 scores on average were observed between subgroups of high and low KUT within EG and CG respectively ($t(8) = -4.82$ for the EG and $t(8) = -4.14$ for the CG, $p < 0.05$, paired t-test, see also **Table 1**). Re-evaluating KUT scores after the last session revealed no significant changes so that in the following sections we will refer to values of the first assessment on day one.

Our main goal was to explore whether the observed differences in individual control beliefs were reflected in differential changes of SMR. Analysis of mean absolute SMR power did not reveal any significant effects over sessions. However, SMR power changed within session as indicated by the significant main effect of run ($F(1, 18) = 4.51, p < 0.05, \eta^2 = 0.20, Obs_{pow} = 0.52$). To further characterize this trend, we applied a linear fit for each group separately (**Figure 1**). While for the CG no trends were found (slope = 0.008, $p = 0.35$, $R^2 = 0.22$, $n = 10$ participants), SMR of the EG consistently increased across runs (slope = 0.023, $p < 0.01$, $R^2 = 0.86$, $n = 10$ participants). As evident in **Figure 1B** this effect was dominated by participants with low KUT scores (slope = 0.035, $p < 0.05$, $R^2 = 0.78$, $n = 5$ participants) who also showed significantly higher SMR values when compared to participants of the EG with high KUT scores ($t(8) = 3.37, p < 0.01$, paired t-test). In contrast, this difference of SMR power between subgroups did not reach statistical significance for the CG ($t(8) = 1.11, p = 0.30$ n.s., paired t-test).

CHANGES OF SMR POWER IN BASELINE

To check for possible lasting effects of NF training we additionally compared baseline SMR power for the different groups. This analysis failed to show modulations across sessions. However, similar to the power changes over runs, we found that participants with lower KUT generally had increased SMR power compared to those with high KUT (**Figure 2B** and **Table 1**). Again, this difference was more pronounced for the EG

Table 1 | Grand average SMR power (in μV^2) of the respective subgroups for electrode Cz across 10 training sessions and while watching the feedback bars (baseline), as well as ratings of control beliefs on day one.

		EG			CG		
		all	low KUT	high KUT	all	low KUT	high KUT
KUT	mean	32.7	29.0	36.4	33.0	29.4	36.6
	SEM	1.4	1.3	0.8	1.5	1.7	0.2
SMR training	mean	2.06	2.66	1.46	1.86	2.23	1.50
	SEM	0.26	0.35	0.09	0.33	0.62	0.23
SMR baseline	mean	1.97	2.46	1.48	1.94	2.39	1.48
	SEM	0.22	0.31	0.05	0.38	0.70	0.22

EG, experimental group; CG control group; KUT, control beliefs while dealing with technology; SMR, sensorimotor rhythm; SEM, standard error of the mean; note that subgroups "low" and "high" of $n = 5$ participants were obtained using median split on KUT scores of "all" $n = 10$ participants.

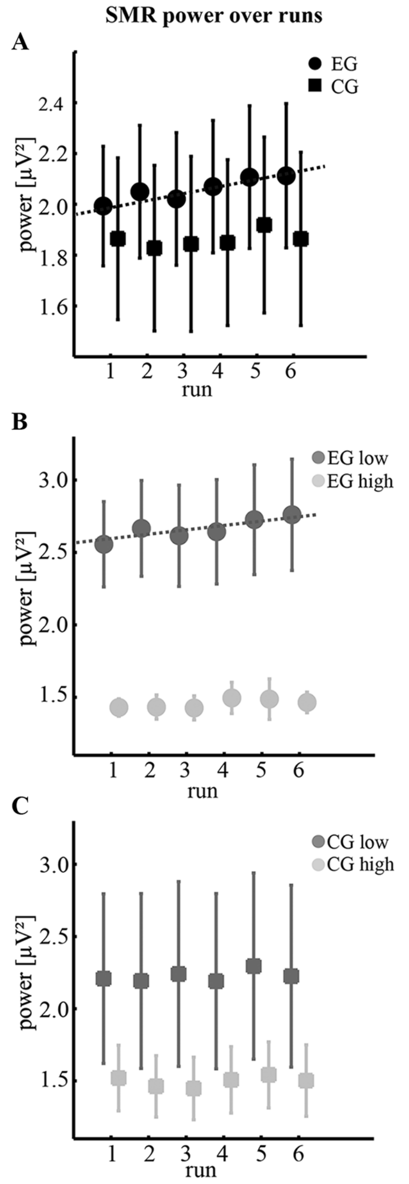

FIGURE 1 | Changes of SMR power during training. **(A)** Mean absolute SMR power (12–15 Hz) across sessions during six runs of neurofeedback training for the experimental group using real feedback (EG, $n = 10$ participants) and the control group using sham feedback (CG, $n = 10$ participants). Dotted line indicates a significant slope of 0.023 μV^2 per run. **(B,C)** Comparison of subgroups ($n = 5$ participants) obtained by median-split according to the individual control beliefs of low and high KUT scores. Dotted line indicates a significant slope of 0.035 μV^2 per run. Note that all error bars represent the standard error of the mean (SEM).

($t(8) = 3.09, p < 0.05$, paired t-test) when compared to the CG ($t(8) = 1.24, p = 0.25$ n.s., paired t-test).

OVERALL CORRELATION OF KUT AND SMR POWER

The results described hitherto all indicate a trend for differences in SMR power between participants of low and high KUT scores. As a direct measure of this relationship we calculated Pearson's linear correlation for both groups. This revealed a significant negative correlation between KUT and overall SMR power during training of $r = -0.69$ for the EG ($p < 0.05$). A strong trend for negative correlation of the same variables in the CG ($r = -0.36, p = 0.31$) was observed, only corrupted by one participant (**Figure 3A**).

As the within group differences in absolute SMR power were also evident in baseline, we additionally evaluated correlation coefficients between KUT and average SMR of these runs (**Figure 3B**). The overall picture was similar to training runs in that participants of the EG showed a negative correlation of $r = -0.73$ ($p < 0.05$) and participants of the CG displayed a similar trend ($r = -0.42, p = 0.23$).

DISCUSSION

As reliable predictors of NF performance still remain elusive, the goal of the current study was to assess whether control beliefs of users correlate with brain activity over several training sessions. Our main results show that voluntary up-regulation of absolute SMR power is more successful in those participants who report a lower subjective level of control while dealing with technology.

This novel finding is supported by several lines of evidence. Firstly, the overall power of SMR in the 12–15 Hz range across ten training sessions negatively correlated with KUT scores for the EG. In other words, participants with lower ratings of control belief were more successful in our training paradigm. According to Krampen (1981) control belief is defined as the individuals' expectancy for a contingent result of an action. The KUT questionnaire quantifies a specific aspect of control, namely how comfortable and confident users feel when interacting with technology (Beier, 2004; Burde and Blankertz, 2006). How this psychological trait may be used to characterize NF performance has remained unexplored so far. Our findings of a negative correlation between KUT and SMR power indicate a higher relaxation in people who subjectively do not expect a major influence on technology. This state of relaxation in turn is known to promote increased SMR amplitudes (Pfurtscheller, 1992; Gruzelier et al., 2006, 2010; Pfurtscheller et al., 2006; Serruya and Kahana, 2008). At the same time our results imply that users with strong control beliefs may try harder to master the feedback paradigm and thus activate resources interfering with the SMR synchronization. This idea of "processing interference" has been proposed in healthy participants and seizure patients (Sterman, 1996, 2000).

In the literature there is only one study that assessed the link between control belief and modulation of brain signals: Burde and Blankertz (2006) reported a positive correlation between KUT and BCI performance. However, their task under investigation and the methods to reveal changes of brain activity clearly differ from our approach. These authors conducted a single session and relied on highly participant-optimized spectro-spatial features for providing feedback. Also they did not directly use the power of SMR for correlation analyses but rather assessed the number of runs in which participants successfully moved a cursor from the center to the target edge of a computer screen. Most importantly, this BCI control implied a motor imagery task where the classified pattern is that of a

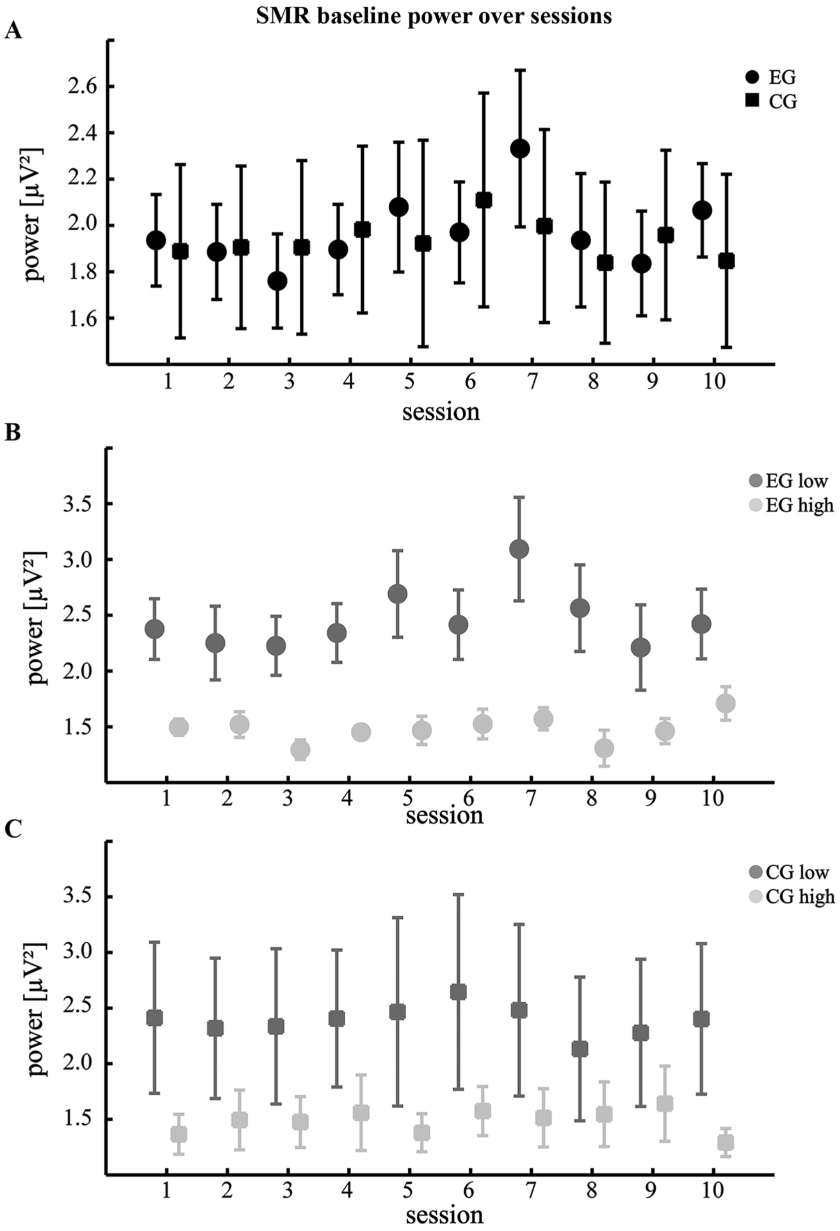

FIGURE 2 | Changes of SMR power during baseline. (A) Mean absolute SMR power across 10 training sessions during the baseline condition. Participants of the EG were watching a visual feedback of their own brain activations without trying to gain control, while participants of the CG were watching a pre-recorded video **(B,C)** comparison according to the individual control beliefs (same conventions as in **Figure 1**).

desynchronization of the SMR. In this light, participants with higher level of control belief could be more successful simply because they will likely try to actively control the feedback and thus down-regulate their SMR stronger during motor imagery. This decrease of activity is also depending on the level of SMR during rest (Blankertz et al., 2010a). In contrast, our NF paradigm directly trained the increase of absolute SMR power. In this task our findings suggest that stronger control beliefs can hinder participants' relaxation and thus an effective up-regulation of SMR power during training. The ability of an individual user to succeed in both up- and down-regulation of SMR may therefore differ based on the different physiological processes and may furthermore depend on the task and method used to evaluate these modulations.

A second aspect of our training in the EG was an increase of SMR power over runs within sessions. Because we applied an online visual feedback, an overall higher level of relaxation may thus have promoted a self-rewarding positive loop. This within session increase is therefore believed to reflect successful training (Vernon et al., 2003; Gruzelier et al., 2006). The fact

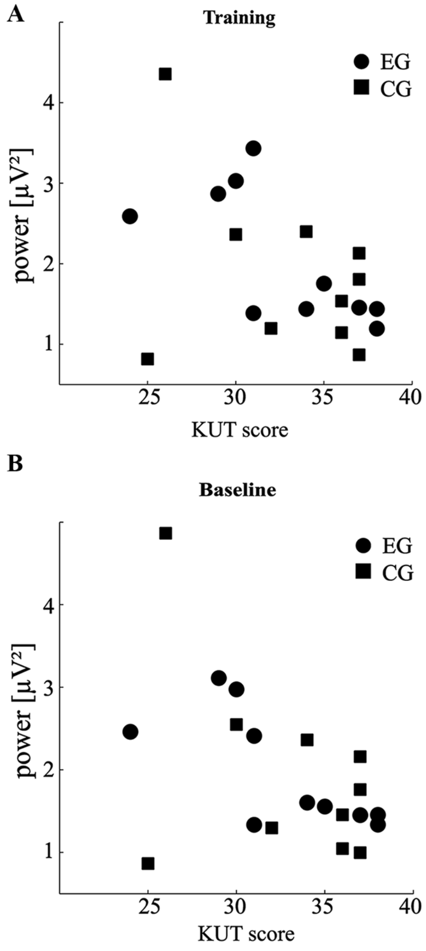

FIGURE 3 | SMR power correlates with control belief. (A) Scatter plot of individual KUT scores against overall SMR power during feedback training (total $n = 60$ runs per participant). **(B)** Same as in **(A)** for baseline runs (total $n = 10$ runs per participant). For details of the relationships please see subsection "Overall Correlation of KUT and SMR Power" in Results.

that absolute SMR power increased only moderately may partly originate from our experimental design: in line with suggestions of other studies (Kubler and Birbaumer, 2008; Nijboer et al., 2010) we adapted the difficulty of our task from run to run in the EG. While this procedure was believed to maintain a high level of motivation and interest in the task, past results also mentioned the risk of incompetence fear (Nijboer et al., 2008). In particular, these authors suggested that when performance in visual SMR feedback is initially high, incompetence fear may hamper further learning. Indeed, we do have evidence for a correlate of negative emotions in insular brain regions during our paradigm (Ninaus et al., submitted to the current special issue). How precisely emotions, task complexity and reward expectancy interact with performance thus needs to be explored in further studies. Interestingly, median split of participants of the EG revealed that those users with low KUT had distinctly higher SMR amplitudes over all runs and showed a significantly increasing trend. In our view, this corroborates the interpretation that control belief is directly linked to the success of SMR feedback training.

It has to be noted however that we did not find any significant modulations or interactions across training sessions. Yet, this does not conflict with past findings as those studies reporting intersession changes either used ratios of the power within two or more frequency bands or relied on relative power changes (Ros et al., 2009; Gruzelier et al., 2010; de Zambotti et al., 2012). In contrast, our measure of absolute SMR power represents a direct index of brain activity. A distinct increase of this index over sessions actually would not have been expected. de Zambotti et al. (2012) recently reported an increase of the SMR-θ ratio across weeks of NF training. However, this ratio was calculated with respect to a baseline and authors mentioned a decrease of SMR-θ in this baseline. As a consequence, the observed training effect in the study of de Zambotti et al. (2012) may not have been solely caused by brain processes in the active period. Our results during baseline did not show a change of SMR power ruling out the possibility of a pseudo training effect. Yet, we again observed a markedly higher SMR for participants of low KUT scores underlining the general validity of this relationship. An important difference to previous work is that during baseline in our approach participants watched feedback bars coupled to their actual brain activity without trying to control the feedback bars. This might explain why overall baseline SMR power was not different to training runs. The role of baseline recordings in assessing changes of power over sessions may thus need further research.

To check for the task-specificity of the observed effects, we included the CG receiving a video of sham feedback. Although the overall SMR power was not significantly different to the EG and since a strong trend for a negative correlation between KUT and SMR was evident, some important points should be considered. First, participants of the CG tended to show lower power values and a higher variance across participants was observed (**Figures 1**,**2**). Second, there was no clear increase of power over runs (**Figure 1C**). And third, the within-group difference between participants of low and high KUT scores was less pronounced than in the EG. Altogether, we thus conclude that in contrast to other studies our CG experienced a residual, although less effective, training as well. This is supported by the fact that no member of this group identified the sham feedback. Instead, the randomized replay of moving bars was accepted as real feedback so that a similar pattern of the relationship between KUT and SMR power emerged. The greater amount of variability and the non-significant dissociation of SMR power between KUT subgroups of the CG suggest, however, that only contingent feedback training can produce clear task-specific effects.

Our findings support the existing NF literature that has suggested a state of relaxed but focused mind for successful performance. For example, a recent study showed a strong inhibition of SMR in initial sessions which was attributed to increased arousal of participants who most likely needed to get used to the experimental setup (de Zambotti et al., 2012). Hammer and colleagues (Hammer et al., 2012) also reported that, besides fine motor skills, the ability to concentrate on the task explained a significant proportion of 19% of the variations seen in BCI performance. At the same time all other psychological parameters, like verbal and non-verbal learning abilities, empathy or mood, did not predict performance in this study. Similarly, motivational factors seem to be only weak predictors of performance and need to be considered at a single subject level (Nijboer et al., 2008, 2010; Kleih et al., 2010). Still, the finding that initial performance during voluntary regulation of brain activity has predictive value (Neumann and Birbaumer, 2003; Kübler et al., 2004) may suggest that personal traits can impact the ability to successfully use feedback paradigms. One important factor in NF and BCI is clearly the individual control beliefs of participants because the tasks per se imply the interaction with technology. The only study in this context we are aware of has already demonstrated a strong correlation between control belief and BCI performance. We clearly extend this knowledge as we identified control beliefs while dealing with technology as a strong predictor of performance in several training sessions. Whether our findings generalize to other frequency-bands and experimental setups needs further validation. In studies that focus on brain activity associated with relaxation, e.g., in treatment of attention deficit hyperactivity disorder, one would expect similar predictive effects. In general, we strongly suggest that concepts of control belief, self-perception and awareness should be considered in more detail during BCI and NF operation.

CONCLUSION

In summary, we demonstrate that control beliefs negatively correlated with the ability to increase SMR during 10 NF sessions. An important implication for future training studies therefore is that participants may not focus on gaining control over the feedback but instead should try to relax themselves. In the light of our results, assessment of individual control beliefs can be used as a predictor of future performance and may thus help to avoid lengthy training.

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Neural substrates of cognitive control under the belief of getting neurofeedback training

Manuel Ninaus*[1], *Silvia E. Kober*[1], *Matthias Witte*[1], *Karl Koschutnig*[1], *Matthias Stangl*[2], *Christa Neuper*[1,3] and *Guilherme Wood*[1]

[1] *Department of Psychology, University of Graz, Graz, Austria*
[2] *Aging and Cognition Research Group, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany*
[3] *Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, University of Technology Graz, Graz, Austria*

Edited by:
Reinhold Scherer, Graz University of Technology, Austria

Reviewed by:
Ranganatha Sitaram, University of Florida, USA
Agnes J. Jasinska, National Institute on Drug Abuse, USA

****Correspondence:***
Guilherme Wood, Department of Psychology, University of Graz, Austria, Universitaetsplatz 2/III, 8010 Graz, Austria
e-mail: guilherme.wood@uni-graz.at

Learning to modulate one's own brain activity is the fundament of neurofeedback (NF) applications. Besides the neural networks directly involved in the generation and modulation of the neurophysiological parameter being specifically trained, more general determinants of NF efficacy such as self-referential processes and cognitive control have been frequently disregarded. Nonetheless, deeper insight into these cognitive mechanisms and their neuronal underpinnings sheds light on various open NF related questions concerning individual differences, brain-computer interface (BCI) illiteracy as well as a more general model of NF learning. In this context, we investigated the neuronal substrate of these more general regulatory mechanisms that are engaged when participants believe that they are receiving NF. Twenty healthy participants (40–63 years, 10 female) performed a sham NF paradigm during fMRI scanning. All participants were novices to NF-experiments and were instructed to voluntarily modulate their own brain activity based on a visual display of moving color bars. However, the bar depicted a recording and not the actual brain activity of participants. Reports collected at the end of the experiment indicate that participants were unaware of the sham feedback. In comparison to a passive watching condition, bilateral insula, anterior cingulate cortex and supplementary motor and dorsomedial and lateral prefrontal areas were activated when participants actively tried to control the bar. In contrast, when merely watching moving bars, increased activation in the left angular gyrus was observed. These results show that the intention to control a moving bar is sufficient to engage a broad frontoparietal and cingulo-opercular network involved in cognitive control. The results of the present study indicate that tasks such as those generally employed in NF training recruit the neuronal correlates of cognitive control even when only sham NF is presented.

Keywords: cognitive control, anterior insula, neurofeedback, fMRI, self-awareness

INTRODUCTION

Neurofeedback (NF) is a kind of biofeedback with the primary goal of helping the user to gain control over specific predefined aspects of his/her brain activity. In typical NF protocols, brain activity is depicted and fed back in real-time to the users. Real-time feedback allows for rewarding desirable patterns of brain activity with visual, auditory or even tactile stimulation and consequently teaching how to control brain activity (Coben and Evans, 2010). NF is employed quite frequently as a treatment for several clinical disorders such as attention and hyperactivity disorders, depression, autism etc. (Lévesque et al., 2006; Angelakis et al., 2007; Coben and Padolsky, 2007; Gevensleben et al., 2009; Niv, 2013). Besides that, NF has become especially interesting for training and improving different cognitive abilities such as working memory and attention (Egner and Gruzelier, 2001, 2004; Vernon et al., 2003; Vernon, 2005). Even sport (Landers et al., 1991) and artistic performances (Gruzelier et al., 2010) are one of the main areas for using NF to enhance performance (Vernon, 2005).

There are several neurophysiological methods to provide NF, such as real-time fMRI, MEG and functional near infrared spectroscopy or even invasive methods such as electrocorticograms (e.g., Kober et al., 2013b; Ruiz et al., 2013b; Sulzer et al., 2013b). For instance, the application of real-time fMRI is growing and evolving rapidly (for reviews see e.g., Ruiz et al., 2013a; Sulzer et al., 2013a). However, especially regarding the feedback speed and the depicted brain signal, EEG NF and real-time fMRI differs significantly (e.g., Sulzer et al., 2013a).

Regardless of which method is employed to provide NF, several aspects of NF learning are constant. An increased degree of attention to the inner state to be learned by NF, a reduction of motor activity and artifacts, general relaxation, concentration, etc., are necessary to learn from NF. Moreover, the usually vague verbal strategies given to participants keep a high degree of similarity across different NF protocols: participants are generally asked to relax and concentrate on the feedback regardless of the exact neurophysiological parameter being trained (Kropotov, 2009). It is recognized that implicit learning mechanisms play an important part in regulating brain activity (e.g., Birbaumer et al., 2013). Birbaumer and colleagues propose that brain-self-regulation is not necessarily an explicit and conscious process and is very similar to skill learning. For instance, real-time fMRI studies show that not only pure operant learning (e.g., Shibata et al., 2012), but also mental imagery and explicit strategies (Kober et al., 2013a,b; Ruiz et al., 2013b) empower participants to self-regulate different brain regions (for reviews see e.g., Birbaumer et al., 2013; Sulzer et al., 2013a). The interplay between skill learning and conscious processes in NF is still poorly understood and the meaning of control over brain activity behind these two processes differs in a very fundamental way. While skill learning describes how specific networks in the brain are modulated by NF on their own activity, explicit processes have a much more general function. Explicit processing and cognitive control may help to calibrate the activation in the rest of the brain through executive processes with the view of not disturbing the networks learning from NF. Hitherto, there is no framework integrating into a unified neurocognitive model this dissimilar collection of aspects of NF learning. In face of the large interest in NF and its good reputation (AAP, 2013), it is necessary that more fundamental principles of NF learning as well as its more general neuronal correlates can be distinguished (Kropotov, 2009).

It is known that explicit learning mechanisms and top-down processes can have a substantial impact on implicit or bottom-up mechanisms (Shallice and Cooper, 2011), however, research on NF is scarce regarding the influence of top-down processing and cognitive control on NF learning. Therefore, in the present study, we aimed to go a step forward toward the understanding of explicit control mechanisms related to NF learning. Particularly, the neural correlates of self-referential processes such as the attention to inner states as well as cognitive control during a NF-like task will be investigated.

A closer inspection of the structure of NF setup reveals that this skill depends directly on focusing attention on internal states. This implies the ability to reduce the attention to external events and concentrate over a determined period of time on internal states. Other cognitive states such as meditation (e.g., Lazar et al., 2005; Farb et al., 2007) and mind wandering (e.g., Mason et al., 2007; Vanhaudenhuyse et al., 2011) are paradigmatic regarding the focusing of attention to internal states. Several studies show that the anterior part of the insula plays a part in attention to and the awareness of internal cues (Barrett et al., 2004; Critchley et al., 2004; Pollatos et al., 2007). Accordingly, learning from NF is most likely dependent on a strong subjective momentary interoceptive sensory process of the participant.

Another central aspect of NF is the perception of control over brain activity. When participants believe to have control over a NF protocol, they refer to the feeling of causing the action, meaning that the participants believe they are able to control the NF in an appropriate way. In the literature this phenomenon is called agency (Gallagher, 2000). Agency plays an important role in self-consciousness and tells us whether an action is caused by ourselves or other entities (Gallagher, 2000; Newen and Vogeley, 2003). Recently, the anterior insula has been identified as a central hub for self-agency (Sperduti et al., 2011). As mentioned above, the primary goal of NF is to gain control over specific predefined aspects of the brain activity. Due to the immediate feedback in conventional NF protocols, self-agency and agency in general, respectively, could play an important part in NF trainings.

Self-referential processes such as agency and self-awareness play an important role in gaining control over brain activity. Therefore, brain regions supporting interoceptive attention such as cingulate cortex, supplementary motor area, dorsomedial and lateral prefrontal areas and especially the insula, as a hub for self-referential processes, can be relevant for NF training because they are involved in the regulation of neuronal activity in many other regions of the brain, which may both favor or hinder NF learning. Evidence suggests that different forms of control (e.g., overcoming cognitive interference, adjusting performance after making an error, inhibiting a prepotent response, regulating one's drug craving, etc.; for reviews see e.g., Miller, 2000; Miller and Cohen, 2001; Kana et al., 2007; Dosenbach et al., 2008; Garavan et al., 2013; Power and Petersen, 2013) engage at least partly overlapping brain networks. So it is plausible that the subjective feeling emerging when one is engaged in a task which demands learning from feedback will be accompanied by the activation in brain areas involved in cognitive control.

To our knowledge, no studies have examined hitherto the neuronal correlates of cognitive control under the belief of training neurofeedback. In this study we examine the cognitive mechanisms and neuronal underpinnings of perceived levels of control over NF applications. In this context, our main goal was to investigate the brain activations observed when participants have the intention to control a moving bar, a task such as those generally employed in NF training. Since we are interested in the neural networks associated with the belief of control in a NF situation and not in the capacity to learn from NF, no real NF protocol was employed in the present study but rather a condition of realistic but fake feedback. In most of the published NF studies, participants do not have a very well specified representation of how to modulate or influence the NF paradigm (e.g., Vernon et al., 2003; Gruzelier et al., 2010; Weber et al., 2011; van Boxtel et al., 2012). For this reason we expected to elicit genuine control beliefs regarding NF regulation in our participants. Sham NF was presented in form of moving bars, which according to instructions were representing participants' brain activity in a very realistic way. To examine neural correlates of participants' attempts to control the NF interface, functional magnetic resonance imaging (fMRI) was employed. Every participant received exactly the same visual feedback. With this methodological approach, we were able to examine the neurophysiological response on the participants' attempt to interact with a NF-like paradigm, independent of individual success rates or better and worse performers in general. Additionally, we were interested in how much control beliefs affect neurophysiological and behavioral correlates of NF learning. For that we have used questionnaires assessing control beliefs while dealing with technology in general.

MATERIALS AND METHODS

PARTICIPANTS

Twenty volunteers [10 male, 10 female, age range 40–63 years; mean age = 46.4 years; standard deviation (*SD*) = 5.14] participated in the experiment after giving informed consent. All participants were naïve to the purpose of the study, had normal or corrected to normal vision and presented no history of major medical illness, neurological or psychiatric disorder, or substance abuse. At the end of the experiment, participants were informed that the feedback presented in fMRI was not related to their brain activation but was a mere recording. The experimental protocol was approved by the ethics committee of the University of Graz.

TASKS

Experimental task

There were three different block designed modeled conditions: in the experimental condition ("get control"), participants were instructed to get control over the movement of the bar by using their brain activity. In the two control conditions, participants were instructed to watch passively the bars. In one control condition ("watch moving bars") the bars were moving like in the "get control" condition and in the other control condition the bars were static ("watch static bars"). Each condition was repeated five times. At the beginning of each trial a cross-hair has been presented for about 18.5 s (jittered from 17 to 20 s). Following this, participants received the visual cues "control" or "watch" for 3 s to get ready for the three different conditions. No action was required in this part of the trial. In the next part of the trial the participants were able to see three different bars. In the "get control"- condition, participants were instructed to try to control the bars during a time interval of 20 s and, at the end of each interval, to rate their perceived success controlling the bars afterwards on a 5-point rating scale (no control—full control). In the "watch moving bars" and the "watch static bars" conditions, participants were instructed to watch passively the screen for 20 s. The timing and the visual appearance of a trial is also shown in **Figure 1**.

The experimental task was conceived to resemble as closely as possible a genuine NF training session. At the beginning of the session, participants were told that they would take part in a training study and that they should use the visual feedback given by a moving bar displayed inside the fMRI scanner to voluntarily modulate their own brain activity according to the feedback. On a feedback screen participants were able to see three different bars (see **Figure 1**). They were instructed to increase the middle bar and decrease the left and right bar. The participants have not received an explicit strategy on how to gain control over the feedback and therefore our approach is comparable with conventional EEG NF instructions (e.g., see Kober et al., 2013a; Witte et al., 2013). The instructions were the same as those our lab uses in the training of SMR frequency in EEG (Witte et al., 2013). Participants were instructed to relax and keep concentrated for the time period of experimental blocks and to use the pauses between them to recover. More specific strategies about how participants were supposed to comply with the instructions were not provided. The visual display was a recording of different sessions of SMR NF training with EEG. Participants were not informed about the exact meaning of the different bars but only that it was important for them to succeed that the central bar should be kept as high as possible and the two lateral bars as low as possible. The animation of the bars was updated 20 times per second and produced by sampling authentic EEG signal of persons undergoing NF training. Therefore, the movements were naturalistic and representative of a typical NF session in both "watch moving bars" and "get control" conditions. Data selected for the production of stimuli were filtered to eliminate movement and eye artifacts. Search for artifacts was conducted by two independent and experienced EEG analysts. This signal was smoothed with a moving average of 1 s so that jumps in signal were avoided. At the moment of fMRI data acquisition, participants were unaware that they got sham feedback. With this methodological approach we were able to examine the neurophysiological response on the participants' efforts to gain control over their own brain activity.

Locus of control for technology

After the fMRI session, participants were asked to fill out several questionnaires. The "locus of control for technology"-questionnaire (KUT; Beier, 2004) was used to assess control beliefs while dealing with technology. The KUT-questionnaire asks the participants to rate, on a 5-point Likert-scale, their handling of technology on 8 items (range of score: 8–40). More precisely the KUT-questionnaire assesses the specific interaction with technical environments of users (e.g., "*I really enjoy finding a solution for technological problems*"; "*Most of the technological problems that I have to face can be solved by myself.*"). The

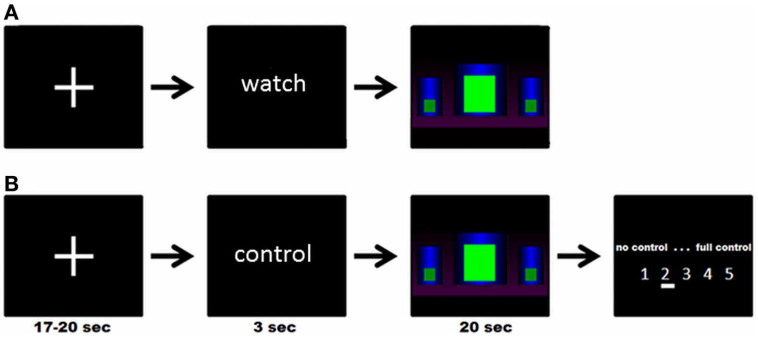

FIGURE 1 | (A) Example of a complete trial of the "watch moving/static bars" condition; **(B)** Example of a complete trial of the "get control" condition; participants were instructed to try to control the movements of the bars during functional MRI measurement.

questionnaire is available in German and has a high reliability ($\alpha = 0.89$; Beier, 1999). Recently, Witte et al. (2013) showed that control beliefs, assessed with the KUT-questionnaire can predict the ability to control a NF. Furthermore, Burde and Blankertz (2006) demonstrated in a BCI-study that the higher the score in the KUT questionnaire was the better was the BCI performance.

Rumination scales

Rumination, a method of coping with negative mood that involves self-focused attention as well as self-reflection (Morrow and Nolen-Hoeksema, 1990; Lyubomirsky and Nolen-Hoeksema, 1993), was assessed with the short version of the Ruminative Response Scale (RRS; Treynor et al., 2003). The RRS is a self-reported measure of rumination consisting of 10 items, and it relates to different components of rumination: reflective pondering and brooding. The first, reflective pondering is an adaptive type of rumination that describes the degree of engagement in cognitive problem solving recruited to improve mood. Depressive brooding is a maladaptive type of rumination which reflects the focus on the meaning and symptoms of distress (De Lissnyder et al., 2012).

MRI DATA ACQUISITION

Neuroimaging data were acquired with a 3.0 Tesla Siemens Skyra MRI scanner at the MRI-Lab Graz (Austria) using a 32 channel head coil and parallel imaging with an iPAT acceleration factor of 2. Functional images were acquired using a T2* weighted gradient-echo pulse imaging sequence (TR = 920 ms; TE = 30 ms, flip angle = 72°; 64×64 matrix; voxel dimensions = $4 \times 4 \times 4$ mm), providing whole brain coverage in 23 slices.

The participants were positioned comfortably in a supine orientation with their head located in the head coil. Foam padding was used around the head to minimize head movements. Participants wore earplugs to reduce discomfort due to scanner noise. Participants viewed the experimental protocol on a screen, via a mirror attached to the head coil. Behavioral measures (ratings) were collected via a MR compatible response box. Participants were required to press the buttons under their index finger and ring finger to navigate through the rating possibilities and to confirm their decision, participants had to press the button under their middle finger.

fMRI DATA ANALYSIS

Functional data were preprocessed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). For the preprocessing of the functional MRI images we used the "MoCo"-series provided by Siemens (Siemens, www.medical.siemens.com), which were corrected retrospectively for intrascan movement. The fMRI-data were then realigned using the first scan as a reference to which all subsequent scans are realigned. Slice time correction was performed. A mean image created from the realigned volumes was spatially normalized to the Montreal Neurological Institute (MNI) EPI brain template (SPM8). The derived spatial transformation was then applied to the realigned and slice time corrected T2* volumes, which were finally spatially smoothed to facilitate group level statistics with a Gaussian kernel of 8-mm FWHM. Statistical models were constructed on the basis of the general linear model implemented in SPM8: all conditions fixation point, cue, "watch static bars," "watch moving bars," "get control," and rating were modeled as block design conditions in a single design matrix. Contrasts were estimated for each participant individually in a first level analysis and statistically tested in second level analyses. Of primary interest for this study were the contrasts of "get control" > "watch moving bars" and "watch moving bars" > "get control." Also reported were the contrasts "watch moving bars" > "watch static bars" and "watch moving bars" < "watch static bars." Whole brain analysis results are reported at a threshold of $p < 0.001$ uncorrected and $p < 0.05$ corrected for multiple comparisons on cluster-level [false discovery rate (FDR)] with a minimum cluster size of 10 voxels. All reported coordinates are reported in MNI space.

RESULTS

BEHAVIORAL RESULTS

Participants had to rate their success controlling the bars on a 5-point rating scale (1 = no control to 5 = full control). The mean rating of success of all participants was 3 (3 = medium control; mean rating = 2.69; *SD* = 0.66; Range: 1–4; **Table 1**). None of the participants reported that they were aware of the sham feedback during a debrief session.

The average score on the KUT-questionnaire of the participants was 31.4 (*SD* = 5.61; Minimum = 20, Maximum = 38). On the RRS questionnaire, participants had an average score of 12.85 (*SD* = 2.98) for the component reflection and 10.35 (*SD* = 2.76) for the component brooding (**Table 1**).

To address the relation between performance rating, control beliefs while dealing with technology and rumination, Pearson correlations were calculated (**Table 1**). A significant negative correlation was found between the performance rating and KUT-scores.

NEUROIMAGING RESULTS

Whole brain analysis results are reported at a threshold of $p < 0.001$ uncorrected in pictures and $p < 0.05$ corrected for multiple comparisons on cluster-level [false discovery rate (FDR)] with a minimum cluster size of 10 voxels in tables. All reported coordinates are reported in MNI space (**Table 2**; **Figure 2**).

To examine the extent to which self-referential processes are relevant for the perceived level of control over a NF-like task, we contrasted the conditions "get control" and "watch moving bars." Importantly, this contrast revealed several highly significant activation clusters. A widespread activation has been identified in frontal areas with its peak in the left anterior part of the insula. Additionally, a large cluster of activation including the right insula dorsomedial and lateral prefrontal and bilateral supplementary motor area as well as the anterior part of the cingulate gyrus. Furthermore, this comparison also revealed significant cluster activation in the right superior parietal lobe, right middle frontal gyrus, left supramarginal gyrus and left thalamus. The corresponding Brodmann areas of these significant activation clusters are listed in **Table 2**. In contrast during the simply watching trials, compared to attempt of controlling the bars, significant activation has been identified only in left angular gyrus (**Table 2**; **Figure 2**).

Table 1 | Correlation between performance rating, control beliefs, and rumination.

Results correlations							**Means**	***SD***
		Rating	**KUT**	**RRS**				
					Reflection	Brooding		
Rating		1.00					2.69	0.66
KUT		−0.46*	1.00				31.40	5.61
RRS		0.01	0.02	1.00			23.20	2.84
	Reflection	−0.16	0.19	0.55*	1.00		12.85	2.98
	Brooding	0.19	−0.18	0.43	−0.51*	1.00	10.35	2.76

KUT, "locus of control while dealing with technology"-questionnaire; RRS, Ruminative Response Scale; $^*p < 0.05$.

Table 2 | Brain regions preferentially activated when attempting to get control over moving color bars compared to when passively watching the moving color bars.

	Brodmann areas	**Voxels**	**Peak**			***T*-value**
			x	***y***	***z***	
"get control" > "watch moving bars"						
L insula *- R insula* *- L precentral gyrus* *- dorsomedial and lateral prefrontal area* *- bilateral supplementary motor area* *- L anterior cingulate gyrus* *- R pars opercularis*	6, 13, 32, 9, 47, 44, 24, 46, 10, 45, 22, 8, 4, 38,	3748	−30	23	1	7.87
R sup. parietal lobe	7	229	18	−64	49	5.60
R middle frontal gyrus	9, 10, 46	110	39	41	40	4.07
L thalamus		149	−15	−10	−2	4.98
L supramarginal gyrus	40	114	−57	−37	34	4.67
"watch moving bars" > "get control"						
L angular gyrus	39	90	−48	−70	28	7.91

Reported coordinates in MNI space; L, left; R, right; $p < 0.001$ *uncorrected on voxel-level,* $p < 0.05$ *corrected for multiple comparisons on cluster-level [false discovery rate (FDR)]; minimum cluster size 10 voxels.*

To determine the general level of activation when participants observed a moving bar, we used the contrasts of "watch moving bars" > "watch static bars" and "watch static bars" > "watch moving bars." A broad network of activation covering the right and left temporo-parietal and inferior frontal areas was observed after subtracting the activity of "watch static bar" from "watch moving bars" (**Table 3**, **Figure 3**).

DISCUSSION

The aim of the present study was to investigate the neural basis of participants' subjective experience when they believe to have control over an external device and use visual feedback. To be able to disentangle the effect of subjective experience from learning from NF, we hold learning rates constant by using sham feedback. Participants were instructed to try to get control over a moving bar presented on the screen in the same way as in a real training session with NF. A large network involving the anterior insula, bilaterally, right operculum, ventral, dorsomedial and -lateral prefrontal cortex, inferior parietal lobule, supplementary motor area and anterior cingulate cortices was more activated when participants actively engaged in the task to move the bar than when they passively watched the bar movements. Moreover, the perceived ability to control the bar during the fMRI measurement correlated negatively with control believes toward electronic devices. In the following, these results will be discussed in more detail.

PERFORMANCE RATING

Debrief performed after the fMRI measurement revealed that no participant questioned the veracity of the feedback obtained in the "watch moving bars" and "get control" conditions. The rating provided by participants after finishing each run of the "get control" condition reveals that participants were actively engaged in the task of trying to get control over the movements of the bar presented on the screen. Average scores in the rating were close to the absolute arithmetical mean of the rating interval employed.

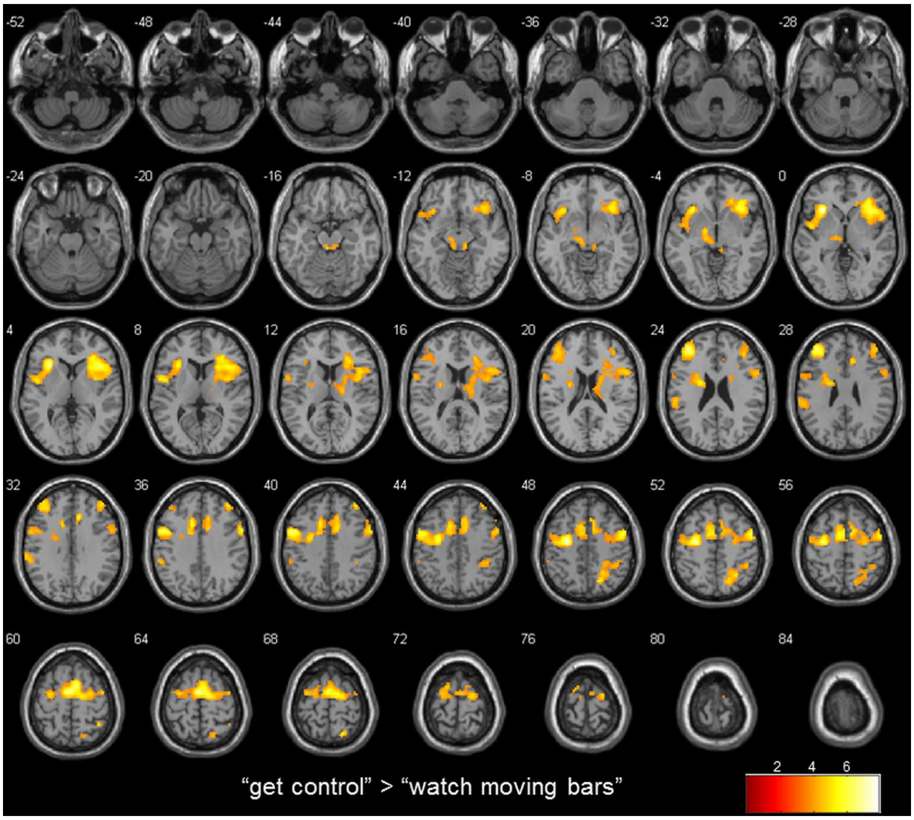

FIGURE 2 | transversal slices (4 mm spacing); t-score map for "get control" "watch moving bars"; $p < 0.001$ uncorrected on voxel-level, $p < 0.05$ corrected for multiple comparisons on cluster-level [false discovery rate (FDR)]; minimum cluster size 10 voxels.

Table 3 | Brain regions preferentially activated when observing moving color bars compared to static color bars (low level control condition).

	Brodmann areas	Voxels	Peak			*T*-value
			x	*y*	*z*	
"watch moving bars" > "watch static bars"						
R temporal cortex, inferior and superior parietal cortex, fusiform gyrus, posterior insula	7, 40, 19, 37, 41, 39, 13, 5, 42, 22	2236	48	−61	1	8.99
L middle occipital gyrus	37, 19, 39	328	−51	−76	1	7.92
L superior parietal lobule	7, 40	364	−30	−52	55	6.05
R inferior frontal gyrus	9, 6, 45, 10, 47, 46, 44, 8	1439	39	23	28	5.89
L supramarginal gyrus	40, 39	280	−60	−52	28	5.15
L precentral gyrus	6, 9, 8	264	−42	−1	52	5.10
"watch static bars" > "watch moving bars"						
No significant activation cluster						

Reported coordinates in MNI space; L, left; R, right; $p < 0.001$ uncorrected on voxel-level, $p < 0.05$ corrected for multiple comparisons on cluster-level [false discovery rate (FDR)]; minimum cluster size 10 voxels.

This can be interpreted as evidence that most participants perceived their ability to control the bar as superior to the chance level. Interestingly, these ratings also were negatively correlated with the control believes toward electronic devices as reported in the KUT scale. These results show that the higher the perceived ability to control electronic devices (i.e., operate a computer or a mobile phone), the lower the perceived ability to control the moving bar during the experiment. Those participants reporting

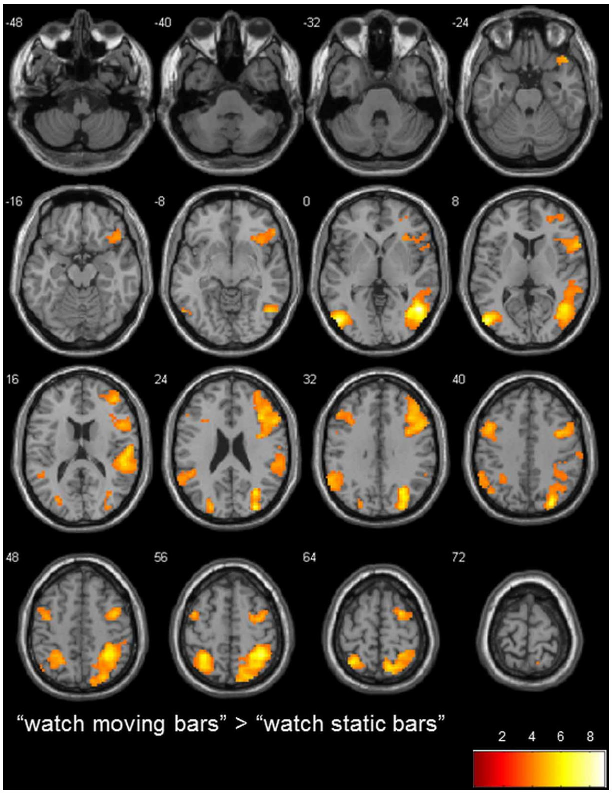

FIGURE 3 | transversal slices (8 mm spacing); t-score map for "watch moving bars" > "watch static bars"; $p < 0.001$ uncorrected on voxel-level, $p < 0.05$ corrected for multiple comparisons on cluster-level (false discovery rate [FDR]); minimum cluster size 10 voxels.

higher control believes toward electronics correctly assessed the levels of control over the bar, which was definitely not under their control, as lower. This suggests that the higher the levels of perceived control reported by participants in general, the higher were also the expectations regarding the capacity to control one's own brain activity and consequently to learn from NF. In participants with high expectations regarding their performance controlling the bar the frustration as expressed by the low ratings was more pronounced. In general, the perception about the general ability to control electronic devices seems to be a determinant of the perceived success of NF learning (see also Witte et al., 2013).

In the present study, most participants reported moderate levels of perceived control over bar movements when in reality they had absolutely no control over it. One could argue that these results are due to the complete absence of valid feedback to participants. However, results from double-blind NF studies (e.g., Witte et al., 2013) reveal that a similar pattern is observed also when real NF is applied. In these studies, most participants receiving either real or sham NF are not able to guess to which group they were assigned even after many successful training sessions. This shows that even when NF is applied, the perception of control is not accurate in NF tasks. To the contrary, perception of control in NF tasks is inaccurate most of the time during training because thresholds are adjusted on a regular basis and individual performance is very variable across sessions. Therefore, it is of primordial interest to detect the brain networks related to believed control. In the following section these results will be discussed in more detail.

THE NEURONAL TOPOGRAPHY OF COGNITIVE CONTROL IN A NEUROFEEDBACK-LIKE PARADIGM

To our knowledge, this is the first study which examines the neural correlates of executive control in a NF-like paradigm using fMRI. In comparison to the control condition "watch static bars," stronger activation in a broad network of regions distributed over the right temporal cortex, inferior and superior parietal cortex, fusiform gyrus, posterior insula, left middle occipital gyrus, left superior parietal lobule, right inferior frontal gyrus, left supramarginal gyrus and left precentral gyrus was observed in the condition "watch moving bars." The activations observed in occipital, temporal and parietal cortex reflect probably the processing of bar movements (Burr and Morrone, 2012), while the activations observed in the inferior frontal gyrus, bilaterally, reflect probably an increase of attention to inner states (Craig, 2009), since in this condition participants were told that they were seeing their own brain activity represented by the moving bar.

To investigate the specific correlates of trying to get control over the bar movements, the conditions "get control" and "watch moving bars" were compared directly. This contrast allows for the interpretation of those neural correlates of cognitive control recruited in situations comparable to NF training uncontaminated by the processing of movement, since the bars moved according to the same principles and in comparable amount in both conditions.

The neuroanatomical structure showing the strongest activation in the contrast "get control" > "watch the bar" was the bilateral anterior insula, which is mainly responsible for driving attention to specific inner states. Our results suggest that the insula is providing the circuitry related to cognitive control with a reference against which to compare the incoming information from visual feedback. Based on the match or mismatch between these two pieces of information, the structures related to cognitive control continuously calibrate cognitive activation in an effort to improve the match between feedback and inner states (Dosenbach et al., 2007). Since feedback was not genuine, the mismatch between inner and external states was constant and cognitive control had to be continuously applied in the "get control" condition. NF learning requires the participants to focus on their own physiological states but the information of their inner state is provided by an external medium (e.g., visual display, auditory feedback etc.). Hence, this process is facilitated by the engagement of cognitive resources dedicated to self-referential processes to integrate this external information into the self.

In other words, the participation of the anterior insula in the present study may be understood as a central hub, which compares and integrates the external information provided by the feedback display with internal information regarding brain activity (Craig, 2009). The feedback, when effective, would enable participants to learn the mental representation of the interrelationship between oneself and the feedback bars in the immediate moment. Therefore, NF could be seen as an embodied tool, meaning that the users embody the provided feedback into their self, in a comparable way as in the BCI literature (e.g., O'Hara et al., 2011; Heersmink, 2013).

Along with the importance of the insula in integrating information provided by the feedback into self-related processes, the participation of anterior cingulate and dorsolateral prefrontal cortex during the "get control" shed further light onto the neural bases of the process of NF learning. NF requires participants to compare the actual state with the desired state of the feedback to be able to learn how to get control over the NF paradigm. The anterior cingulate cortex is known to be associated to detect discrepancies between an actual and a desired state (Carter et al., 2000; Kerns et al., 2004), self-reflection (Herwig et al., 2012) and to tuning attentional processes (Bishop et al., 2004) with direct connections to thalamus, insular cortex, amygdala, parietal and prefrontal areas (Goldman-Rakic, 1988). Describing these functions of the anterior cingulate cortex highlights the importance of this region for NF regardless of the content of specific NF training programs.

ATTENTION-NETWORK UNDER THE BELIEF OF GETTING NEUROFEEDBACK TRAINING

Besides the increase in bilateral insula activation during the "get control" condition, activation in the right pars opercularis of the inferior frontal gyrus and right middle frontal gyrus was observed. In several studies, those two regions are associated with stimulus-driven attention and the maintaining of attention (e.g., Corbetta and Shulman, 2002; Weissman et al., 2006). Furthermore, the whole brain analysis revealed activation in several regions associated with cognitive control, such as dorsomedial and lateral prefrontal areas. During the "get control" condition, participants had to sustain their attention toward internal and external sources over a period of time. Along with the identified activation in right pars opercularis, and right middle frontal gyrus and dorsomedial and lateral prefrontal areas we have found activation in a brain structure closely associated with the left thalamus. Those brain areas are critical for processing internal states (Miller and Cohen, 2001) and therefore could play a critical role in acquiring control over a NF paradigm. Further evidence that the participants were highly engaged in acquiring control over the bars and shifted their attention toward the sham NF is the significant bilateral activation in the supplementary motor area, especially in context with the significant activation in anterior cingulate cortex and thalamus during the "get control" condition. Those regions provide signals that support the brain's moment-to-moment information processing and form a centralized control system (Dosenbach et al., 2007). Regarding our paradigm, where participants had to constantly integrate the provided information from the moving bars, the identified regions apparently play a major role in driving the regulation of inner states with the aim of regulating the movements of the bar. However, we cannot rule out that the bilateral activation in the supplementary motor area emerged due to anticipation of motor response during the "get control" condition since participants were asked to rate their performance after the feedback in the "get control" condition.

LEFT ANGULAR GYRUS

The contrast between "watch moving bars" and "get control" condition revealed only one significant activation cluster with its peak in the ventral part of the left angular gyrus. Seghier (Seghier et al., 2010; Seghier, 2013) proposed that this part of the left angular gyrus is associated with the default mode network. Therefore, left angular gyrus is prominent during rest and when persons are not engaged in external interactions (Buckner et al., 2008) and is interrupted during effortful tasks (Binder et al., 1999; Seghier et al., 2010). Our result implicates that the participants did not try to gain control or interact with feedback during the "watch moving bars" condition, which supports our experimental setup.

However, a meta-analysis about different brain structures related to self- and external-agency conducted by Sperduti and colleagues (Sperduti et al., 2011) revealed that the left angular gyrus is also part of the external agency attribution network. During the "watch moving bars"-condition the participants may have experienced that the displayed moving bars are rather not caused by them than during the "get control" condition.

CONTROL BELIEFS MAY INFLUENCE NEUROFEEDBACK LEARNING

As outlined so far, NF training is linked to interoceptive and self-referential processes. In contrast to NF trainings, in most of the brain computer interface studies participants get a quite concrete instruction about how they are able to control the interface or what mental task they should use. The common mental tasks are motor imagery, mental subtraction etc. (e.g., Friedrich et al., 2012) to yield highly distinguishable brain patterns. It has been shown that control beliefs toward technology can be used as a predictor of brain computer interface performance. Burde and Blankertz (2006) showed that the higher the KUT results were the better was the brain computer interface performance. Due to the fact that gaining control over a NF especially in the early stages of a training mostly relies on "trial-and-error" learning and that the participants do not receive a concrete instruction about how to modulate the NF paradigm, it is not surprisingly that the KUT score in the present study negatively correlates with ratings of the participants after a "get control" trial. Participants with a higher KUT score may expect that they are able to deal well with the NF paradigm form the beginning. These participants have the most reasons to be disappointed with their performance and therefore rate their success to control the NF lower than participants with a lower KUT score and lower expectations regarding the outcome (see also Witte et al., 2013). These findings could also imply that participants who are highly convinced handling technology well struggle the most with getting control over a NF. In a recent study, Kober et al. (2013a) showed that some strategies employed by NF participants may lead to a cognitive overload, which prevents NF learning. Due to the repeated attempts by those persons to get control over the NF, they may impede themselves by trying too hard and are therefore not able to direct their attention on the quite subtle internal bodily cues, especially at the early stages of the training.

SUMMARY

In summary, we used fMRI to identify brain regions associated with believed control in a task similar to NF learning. Because of the use of sham feedback only, the activations observed in the present study are due to differences in believed control and were not affected by specific NF learning processes. The significant activation in the anterior insular and cingulate cortex suggests that participants actively tried to get control over the moving bar in the "get control" condition. Behavioral data additionally showed a negative correlation between the subjective estimates about the amount of control perceived in the "get control" condition and control beliefs.

The present study reveals the neuronal networks related to general regulatory processes associated with NF settings. We assume that especially regions relevant for self-referential processes such as self-awareness and self-agency play an important part in acquiring control over a NF, due to the fact that participants have to focus on their own physiological signals, which requires a big amount of self-referential cognitive load.

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Modulation of functionally localized right insular cortex activity using real-time fMRI-based neurofeedback

Brian D. Berman[1,2]*, **Silvina G. Horovitz**[2] and **Mark Hallett**[2]

[1] Department of Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[2] Human Motor Control Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

Edited by:
Guilherme Wood, Karl-Franzens-University of Graz, Austria

Reviewed by:
Elise Klein, Knowledge Media Research Center, Germany
Andrea Caria, University of Tuebingen, Germany

***Correspondence:**
Brian D. Berman, Department of Neurology, University of Colorado Anschutz Medical Campus, 12631 East 17th Avenue, Mail Stop B-185, Aurora, CO 80045, USA
e-mail: brian.berman@ucdenver.edu

The capacity for subjects to learn to volitionally control localized brain activity using neurofeedback is actively being investigated. We aimed to investigate the ability of healthy volunteers to quickly learn to use visual feedback during real-time functional MRI (rtfMRI) to modulate brain activity within their anterior right insular cortex (RIC) localized during a blink suppression task, an approach of possible interest in the use of rtfMRI to reduce urges. The RIC region of interest (RIC-ROI) was functionally localized using a blink suppression task, and blood-oxygen level dependent (BOLD) signal changes within RIC-ROI used to create a constantly updating display fed back to the subject in the scanner. Subjects were instructed to use emotional imagery to try and increase activity within RIC-ROI during four feedback training runs (FB1–FB4). A "control" run (CNTRL) before training and a "transfer" run (XSFR) after training were performed without feedback to assess for baseline abilities and learning effects. Fourteen participants completed all neurofeedback training runs. At the group-level, increased BOLD activity was seen in the anterior RIC during all the FB runs, but a significant increase in the functionally defined RIC-ROI was only attained during FB2. In atlas-defined insular cortex ROIs, significant increases were seen bilaterally during the CNTRL, FB1, FB2, and FB4 runs. Increased activity within the insular cortices did not show lateralization. Training did, however, result in a significant increase in functional connectivity between the RIC-ROI and the medial frontal gyrus when comparing FB4 to FB1. Since neurofeedback training did not lead to an increase in BOLD signal across all feedback runs, we suggest that learning to control one's brain activity in this fashion may require longer or repeated rtfMRI training sessions.

Keywords: neural modulation, real-time fMRI, biofeedback, insular cortex, urges

INTRODUCTION

Technological advances in computer hardware and functional MRI (fMRI) data processing software have made it possible to analyze neural activity as measured by changes in blood-oxygen level dependent (BOLD) contrast almost as quickly as images are acquired. This real-time fMRI (rtfMRI) approach allows for the displaying of measures of localized brain activity back to a subject in a scanner and investigation of their ability to learn to volitionally control their own brain activity (deCharms, 2007; Weiskopf et al., 2007; Weiskopf, 2012). The use of such rtfMRI-guided neurofeedback offers significant advances over traditional biofeedback with evaluation involving whole brain coverage, good spatial resolution, and ability to target specific brain regions in a given patient.

An increasing number of rtfMRI studies have been reported suggesting that healthy subjects can learn through operant training to use neurofeedback to control the activity in a wide range of cerebral regions. These regions include the anterior cingulate cortex (Weiskopf et al., 2003; deCharms et al., 2005), right inferior frontal gyrus (Rota et al., 2008), and auditory cortex (Yoo et al., 2006), as well as the difference between activation in supplementary motor area and parahippocampal place area (Weiskopf et al., 2004) and in motor-associated cortices during motor tasks (Posse et al., 2001; Yoo and Jolesz, 2002) and during motor imagery tasks (deCharms et al., 2004; Yoo et al., 2004, 2007, 2008; Berman et al., 2012b). In addition to these brain regions, rtfMRI-based modulation of limbic-associated brain regions has also been demonstrated in neurofeedback studies involving the amygdala (Posse et al., 2003; Zotev et al., 2011) and insular cortex (Caria et al., 2007, 2010; Johnston et al., 2010; Ruiz et al., 2011; Veit et al., 2012).

Recently, rtfMRI-based neurofeedback has demonstrated the potential to lead to clinical effects in certain patient populations. Preliminary studies suggest neurofeedback may have benefit in patients suffering from chronic pain (deCharms et al., 2005), tinnitus (Haller et al., 2010), depression (Linden et al., 2012), and Parkinson disease (Subramanian et al., 2011). One study found that patients with schizophrenia showed improved performance on a face recognition task after neurofeedback training focused on modulating insula activity (Ruiz et al., 2011). Although Tourette syndrome has shown some success in treatment with biofeedback and EEG-guided neurofeedback training (Tansey, 1986; O'Connor et al., 1995; Piacentini

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Abbreviations: AFNI, Analysis of Functional NeuroImages; BOLD, blood-oxygen level dependent; CNTRL, "control" scanning run; FB, "feedback" scanning run; FOV, field of view; RIC, right insular cortex; ROI, region of interest; rtfMRI, real-time functional MRI; XSFR, "transfer" scanning run.

and Chang, 2001; Heinrich et al., 2007; Messerotti Benvenuti et al., 2011), the use of rtfMRI-guided neurofeedback to treat Tourette syndrome has, to the best of our knowledge, not been reported.

A number of imaging studies from our lab and other investigators have supported the presence of abnormal limbic-motor coupling in patients with the neuropsychiatric disorder Tourette Syndrome (Jeffries et al., 2002) as well as involvement of the insular cortex during tic initiation and execution (Stern et al., 2000; Bohlhalter et al., 2006; Lerner et al., 2007). Given the association of insula activity with tic generation in Tourette syndrome, and since tic performance is frequently preceded by a premonitory urge (Kwak et al., 2003), learned modulation of insular cortex activity through rtfMRI-guided neurofeedback training could provide an effective approach by which patients could learn to consciously inhibit the onset of a tic. The insular cortex might also be an especially good target for self-modulation as it has been shown to be involved in a wide range of functions including sensory perception and integration, motor control, and emotive and cognitive functioning, in addition to self-awareness and interpersonal experience (Craig, 2002).

In the present study, we sought to develop and establish an rtfMRI-based neurofeedback training methodology that could be used for future investigation as a therapeutic intervention in neuropsychiatric conditions associated with disordered suppression where a role for the insular cortex has been implicated such as Tourette syndrome (Bohlhalter et al., 2006; Lerner et al., 2007; Fahim et al., 2009), obsessive–compulsive disorder (Nishida et al., 2011; Stern et al., 2011), eating disorders (Kim et al., 2012; Lawson et al., 2012), and post-traumatic stress disorder (Nagai et al., 2007; Herringa et al., 2012). We first chose to specifically target the anatomic region of the anterior right insular cortex (RIC), which supports a representation of visceral responses thought to be accessible to awareness (Critchley et al., 2004). We employed an eye blink suppression task to refine the location of the targeted region for neurofeedback to an area that is associated with urge suppression (Berman et al., 2012a). Blink suppression was used for functional localization because blinking is often one of the earliest manifestations and most common tics in Tourette syndrome and because the buildup of the urge to during blink inhibition and the relief that accompanies their eventual performance can serve as a model for the buildup of uncomfortable sensations that commonly precede tics (Shapiro et al., 1988; Peterson and Leckman, 1998).

Given that the preferential recruitment of the insula during tasks involving recall and imagery of emotionally relevant events (Phan et al., 2002), along with the success of recent rtfMRI studies involving modulation of right anterior insular cortex activity with thoughts with emotional valence (Caria et al., 2007, 2010), our study participants were instructed to use cognitive strategies that focused on emotional induction by recall or imagery of emotionally relevant events during neurofeedback training. We hypothesized that healthy volunteers would be able to learn how to self-modulate neural activity within their anterior RIC that is functionally localized to a region specifically involved during the suppression of blinking using rtfMRI-guided neurofeedback.

MATERIALS AND METHODS

PARTICIPANTS

We enrolled a total of sixteen healthy volunteers, aged 29.3 ± 7.8 years (9F, 7M). All participants had normal neurological examinations and all but one were right-handed by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the Combined Neurosciences Institutional Review Board of the National Institutes of Health, and all participants gave their written informed consent before participation.

IMAGING DATA ACQUISITION

Images were acquired with a 3T scanner and 8-channel head coil (GE Signa, Milwaukee, WI, USA) foam-padded to restrict head motion and improve subject comfort. Functional T2*-weighted images were acquired using gradient echo, echo planar imaging using the imaging acquisition parameters: matrix size = 64 × 64, field of view (FOV) = 22 cm × 22 cm, TR = 1000 ms (800 ms for first six subjects), TE = 30 ms, flip angle = 70°, bandwidth = 250 kHz. Each scan consisted of 14 or 17 slices that covered most of the brain except for the cerebellum (3.3 mm × 3.3 mm nominal in-plane resolution, 5.0 mm thick slices, 0.5 mm gap). High-order shimming was applied to lessen the field inhomogeneities during data collection and improve the signal-to-noise ratio in areas prone to susceptibility artifacts. A high-resolution magnetization-prepared rapid gradient echo anatomical scan was acquired for each subject for superposition of functional maps upon brain anatomy and to allow for image normalization to a standardized brain space (matrix size = 256 × 256, FOV = 22 cm × 22 cm, 1 mm^3 isotropic resolution, TR = 10 ms, TE = 4.96 ms, flip angle = 19°).

FUNCTIONAL LOCALIZATION OF ANTERIOR RIGHT INSULAR CORTEX

Real-time fMRI data were acquired and exported in real-time to a console at the scanner running Analysis of Functional NeuroImages (AFNI) software (Cox, 1996), which allowed for real-time motion correction and monitoring of a continuously updating BOLD signal time-course display. During the functional localization scanning run, participants were instructed to inhibit eye blinking during three 60-s time periods (**Figure 1A**). Simultaneous electrooculography was used to ensure subjects were suppressing blinking (see methods in Berman et al., 2012a). A 5 × 5 voxel (16.5 mm × 16.5 mm) square region of interest (ROI) in the axial plane was initially positioned through the use of anatomical landmarks such that it was placed in the area of the anterior RIC (**Figure 1B**). BOLD signal responses during the blink suppression run were then explored in all three dimensions in the vicinity of the anatomically derived position of the ROI until a position was found that visually led to the maximum amount of buildup in BOLD signal in the ROI during the blink suppression blocks (**Figure 1C**). A composite map of the RIC-ROI for all subjects, created by summing RIC-ROI masks with each assigned a value of 1 and co-registered to a standard stereotactic space (Talairach

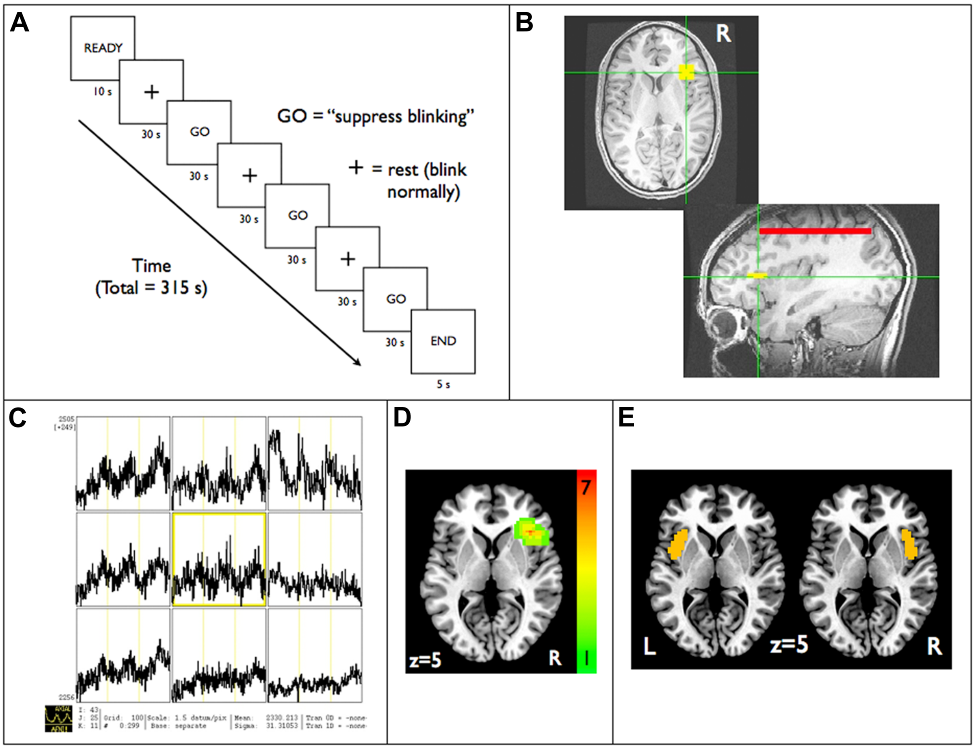

FIGURE 1 | Functional localization of the anterior RIC: **(A)** real-time fMRI scanning paradigm used for blink suppression task. RIC-ROI (5 × 5 voxels, yellow square) is first **(B)** localized by using anatomical landmarks and then **(C)** centered on the axial slice and voxel that maximized increases in BOLD signal within the ROI that corresponded temporally to the blink suppression blocks. Also shown is **(D)** a composite map that demonstrates the functionally localized ROIs were clustered around anatomical location of RIC and **(E)** the left and right anterior short insular gyrus anatomical ROIs defined using the Destrieux atlas, both displayed on standard axial brain slices in Talairach space. Red line shown in **(B)** is a reference ROI encompassing the entire brain volume in an axial slice distant to the RIC-ROI used in generating the neurofeedback display (see text). RIC, right insular cortex; ROI, region of interest.

and Tournoux, 1988), revealed a distribution of the ROIs clustered around the anatomical location of the RIC with maximum overlap of seven subjects' RIC-ROI masks (**Figure 1D**).

REAL-TIME NEUROFEEDBACK DISPLAY

A reference ROI (REF-ROI) encompassing the entire brain volume in an axial slice distant to the insular cortex ROI (see example red line, **Figure 1B**) was used to average out any unspecific activation and cancel out non-specific activation and global scanning effects. The mean BOLD signal within the specified ROIs were extracted and exported in real-time to a dedicated Linux workstation. In-house Python routines were developed to read BOLD signal changes, perform basic mathematical operations, and produce a dynamic visual display that conforms to standard block fMRI experimental design. The feedback display consisted of a red column with a height that was continuously updated after an initial baseline rest block at each TR using the following equation:

$$\text{Column height (TR)} = \frac{[\text{RIC} - \text{ROI (TR)}\,/\text{RIC} - \text{ROI (baseline)}]}{[\text{REF} - \text{ROI (TR)}\,/\text{REF} - \text{ROI (baseline)}]}$$

The feedback display also contained a solid bar at the top to represent the target level of activity, a dashed line representing the average level of activity measured during the baseline rest block, and an arrow to emphasize the direction brain activity is to be modulated.

NEUROFEEDBACK TRAINING

Two types of scanning runs were used during neurofeedback training with tasks presented in a block-design fashion (**Figure 2**). During the feedback runs ("FB"), participants were shown a continuously updated feedback display and instructed to increase the red column's height toward the goal bar by focusing their thinking on recall or imagery of emotionally relevant events – a mental task based on a previously reported demonstration of subjects to use this strategy during neurofeedback training to modulate activity within the anterior RIC (Caria et al., 2007, 2010). The specific verbal instruction given to each subject to help guide their feedback strategies was for the subject to "focus on imagery or recall of emotionally relevant thoughts or memories." During the "GO" runs, participants only saw the word GO on the screen and were instructed to perform the emotional imagery task in the absence of any visual feedback.

Each scanning run began with 10 s for scanner signal stabilization and participant acclimation to the scanner environment before an initial 30 s baseline rest block. The active GO and FB blocks were alternated with rest blocks during which participants

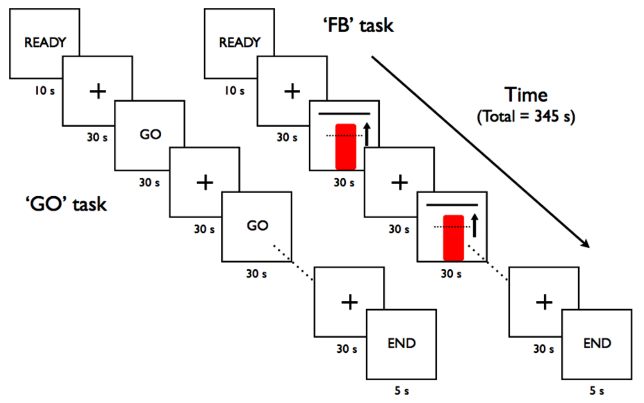

FIGURE 2 | Block-design task paradigms for the rtfMRI-based scanning runs.

were encouraged to relax and think of the letters "A, B, C" or numbers "1, 2, 3" in order to divert their focus from the emotional mental imagery used during the active blocks of the scanning runs. Each scanning run consisted of a total of the initial baseline rest block followed by five active regulation blocks (GO or FB) separated by rest blocks of 30 s each (**Figure 2**). A final 30 s rest block allowed the delayed hemodynamic response from the final active block to be included in the analysis.

Immediately prior to scanning, participants were instructed in the layout of the scanning runs outlined above and informed of the inherent hemodynamic delay in addition to an approximate additional 1 s delay required to process imaging data and update the neurofeedback display. Scanning runs for each subject consisted of an initial pre-training "control" GO run (CNTRL), followed by four FB training scanning runs (FB1–FB4), and a final post-training or "transfer" GO run (XSFR). The CNTRL run was performed to evaluate the ability of participants to modulate activity within the RIC-ROI before neurofeedback training and the XSFR task was performed to evaluate if neurofeedback training led to the ability of participants to modulate brain activity in the RIC-ROIwithout the presence of neurofeedback. After each of the scanning runs, participants were asked to briefly describe the type of emotional imagery they used during the previous run (with or without feedback). If the emotional imagery was of a personal nature, participants were informed they did not have to answer the question.

OFF-LINE IMAGE ANALYSIS

Images were analyzed *post hoc* using AFNI and the *afni_proc.py* processing stream. The first 10 scans of each session were excluded from data analysis to account for T1 equilibration effects and subject scanner acclimation. Functional scanning images were corrected for motion and realigned using the last scan as a reference (closest to anatomical scan acquisition). Images were spatially smoothed using an isotropic 8-mm FWHM Gaussian filter to accommodate individual anatomical variability. The realigned images were co-registered to the high-resolution anatomical images and subsequently transformed into Talairach space (Talairach and Tournoux, 1988).

Task-related changes in BOLD signal at the individual level were estimated at each voxel using a block-design function convolved with a standard gamma-aviate hemodynamic response function and a general linear model (GLM). Covariates derived from motion parameters were included into the GLM to take into account artifacts caused by head motion. Group-level analysis was performed using a simplified mixed-effects model (one-sample t test) to test for within-group differences in task-related changes in BOLD. Family-wise error (FWE) correction for multiple comparisons was performed using Monte Carlo-based simulations with the AFNI program *3dClustSim*. We set overall significance at $p \leq 0.01$ FWE corrected by using a voxel threshold of $p \leq 0.005$ and a cluster size threshold of 113 voxels.

ROI ANALYSIS

The functionally localized RIC-ROI for each subject was used to perform hypothesis-driven ROI analysis for each neurofeedback scanning run. BOLD times series used for the ROI analysis were extracted from imaging data that had undergone the same preprocessing steps as used for the whole brain analysis. The mean percent signal change between the active and rest blocks for all GO and FB runs was calculated for each subject separately and then averaged across subjects. Group-level analysis also included an evaluation of training effects using a one-way repeated measures ANOVA (Prism 6.0) to assess treatment effect across all six training runs and across the four FB training runs across subjects, and paired t tests for XSFR vs. CNTRL and FB4 vs. FB1. Significant increases in mean percent BOLD signal above a resting baseline for each neurofeedback run were also evaluated using paired t tests. Significance level threshold for the t tests and repeated measures ANOVA was set at $p \leq 0.05$.

Exploratory ROI analyses were also performed including assessing the "best performers" and the "best performances." The "best performers" were evaluated because it is unlikely that all participants are able to quickly learn to use rtfMRI-guided neurofeedback to modulate brain activity within a relatively short training period. The "best performances" were evaluated to assess if a particular themes in the types of emotional imagery found to be most successful in increasing the activity in RIC-ROI could be identified. The "best performers" group included those participants who had a significant increase in BOLD signal during neurofeedback blocks for at least two of the four FB runs. The "best performances" included the top third performances for each neurofeedback scanning run independent of the participant. Paired and one-sample t tests were used to evaluate XSFR vs. CNTRL, FB4 vs. FB1, and increases in mean percent BOLD signal above a resting baseline for each neurofeedback run for the "best performers" and "best performances," respectively. The emotional valence of each subject's self-reported emotional imagery was also used to test whether negative or positive emotional valence was associated with better neurofeedback performance. Details of self-reported imagery were further assessed for similar themes and grouped in order to compare the effects of specific mental strategies in their ability to lead to significant increases in RIC-ROI over baseline during the neurofeedback runs. Significance level for t test comparisons was set at a threshold of $p \leq 0.05$.

Structurally defined right and left anterior insular cortex ROIs were used to investigate BOLD signal changes within the greater anterior insular cortex volumes during neurofeedback and to assess for laterality effects during neurofeedback training. These ROIs were defined using the anterior short insular gyrus as derived from probabilistic labeling of the SPM (http://www.fil.ion.ucl.ac.uk/spm/) single subject average image based on the Destrieux atlas in Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Both ROIs were smoothed using an 8 mm FWHM kernel analogous to that used for the rtfMRI data analysis and then intensity filtered to limit the overall size of the ROI, approximate the structures in Talairach space, and minimize artifactual increases in statistical thresholds due to large surface areas relative to volumes (see **Figure 1E**). A lateralization index (LI) was calculated for each subject using a normalized difference between percent signal change extracted from the target (%RIC) and contralateral ROI (%LIC) using the equation: $\text{LI} = (\%\text{RIC} - \%\text{LIC})/(\%\text{RIC}+\%\text{LIC})$, as has been applied elsewhere (Caria et al., 2007).

CONNECTIVITY ANALYSIS

The residual BOLD times series from the whole brain analysis were used for the connectivity analysis to assess whether neurofeedback training altered underlying connectivity between RIC-ROI and another brain region. For each run and each subject, the time series of the functionally localized RIC-ROI was used as seed and correlated with each voxel in the brain. Individual correlation maps were then transformed into Talairach space (Talairach and Tournoux, 1988), and r values were Fisher transformed to z-scores before performing group analysis. Group-level connectivity maps for each of the neurofeedback training runs were generated. Voxel-wise connectivity changes were then investigated between CNTRL run and the XSFR run and between FB1 and FB4. Overall significance was set at $p \leq 0.01$ FWE corrected by using a voxel threshold of $p \leq 0.005$ and a cluster size threshold of 113 voxels. We then extracted cluster statistics for each subject and each run using a mask generated from the significant clusters identified in the group-level connectivity map and tested them for changes using a repeated measures one-way ANOVA and paired t tests (Prism 6.0).

RESULTS

PARTICIPANTS

One participant was unable to remain still during the neurofeedback runs and had to have her scanning terminated. Technical scanner issues forced neurofeedback scanning to be terminated shortly after starting neurofeedback training in another participant. Thus, 14 participants (aged 29.7 ± 8.2 years; 8F, 6M) completed all four FB runs were included in the final analysis. Software glitches resulted in two of the14 participants not having usable CNTRL runs and one not having a usable XSFR run such that 12 CNTRL runs and 13 XSFR runs were available for final analysis.

FUNCTIONAL LOCALIZATION OF ANTERIOR RIC

Fifteen participants completed the functional localizer blink suppression scanning and simultaneous electrooculography confirmed all participants were attempting to suppress blinking during functional localization run (see Berman et al., 2012a). Regions were identified for all participants within the vicinity of the anterior RIC that exhibited signal increasing BOLD signal responses consistent with the blink suppression blocks (see **Figure 1C**).

NEUROFEEDBACK TRAINING

Group-level voxel-wise analysis (**Figure 3**, **Table 1**) revealed significantly increased BOLD activity within the region of the anterior RIC during all four training scanning runs when visual neurofeedback was provided (FB1–FB4), but not when there was no visual feedback (CNTRL and XSFR). Reported cognitive strategies employed by participants included both positive mental imagery (e.g., walking through the woods, lying on a beach, traveling, planning a party, and imaging actions of a character in a book),

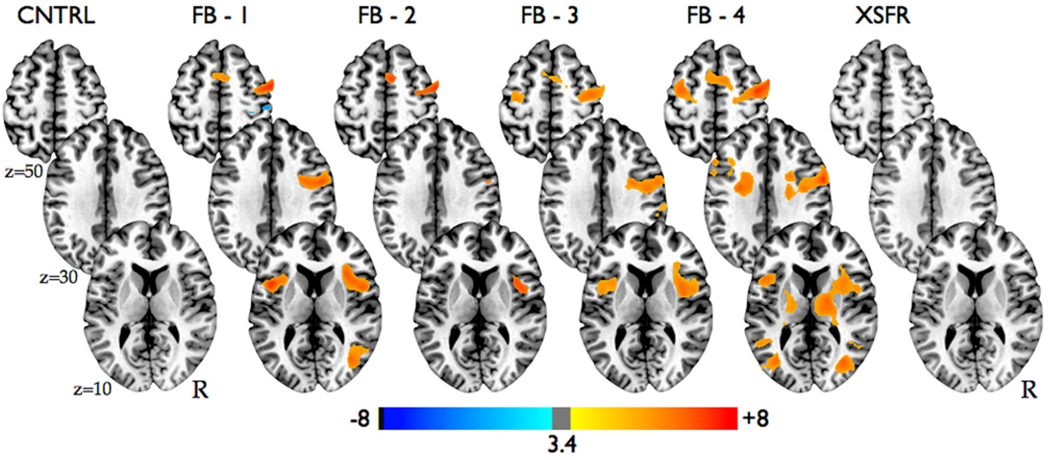

FIGURE 3 | Statistical parametric maps showing significant activation changes from baseline during all neurofeedback training runs in all participants (n = 14). Images are shown at $p \leq 0.01$, FWE corrected, on axial slices of a standard brain in Talairach space.

Table 1 | Brain areas with significant activation changes during neurofeedback training.

Task	Cluster size (voxels)	Side	Region (Brodmann area)	Talairach coordinates			Peak *t* value
				X	*Y*	*Z*	
CNTRL	383	R	Precuneus (19), inferior parietal lobe (40)	32	−70	38	−6.06
FB 1	1049	R	Precentral gyrus (4,6), anterior insula, inferior frontal gyrus (6,44)	50	−4	44	7.74
	407	L/R	Medial frontal gyrus (6)	−10	−1	62	6.76
	308	L	Anterior insula	−40	8	5	7.00
	220	R	Middle occipital gyrus (19)	35	−64	5	6.45
	168	R	Postcentral gyrus (3)	38	−31	56	−4.45
FB 2	459	R	Precentral gyrus (6), anterior insula, inferior frontal gyrus (6,44)	50	−4	44	5.61
	155	L/R	Medial frontal gyrus (6)	11	−4	59	5.08
FB 3	1628	R	Precentral gyrus (6), anterior insula, inferior frontal gyrus (6,44), medial frontal gyrus (6)	38	−13	38	8.37
	234	L	Anterior insula, inferior frontal gyrus (44)	−40	2	5	4.63
	147	R	Postcentral gyrus (2), inferior parietal lobe (40)	65	−28	41	4.27
	133	L	Middle frontal gyrus (6), precentral gyrus (6)	−28	−7	38	4.89
FB 4	3925	L/R	Middle frontal gyrus/precentral gyrus (6), anterior insula, medial frontal gyrus (6), inferior frontal gyrus (6,9), thalamus, putamen	38	−7	44	7.50
	283	L	Middle occipital gyrus (19), middle temporal gyrus (39)	32	−67	11	5.75
	240	L	Middle occipital gyrus (19), superior temporal gyrus (39)	−31	−67	8	4.85
XSFR	None						

as well as negative imagery (recalling emotional or bad memories, remembering an argument, and focusing on someone close dying). Cognitive strategies that were associated with the best performances during neurofeedback training included both negative and positive mental imagery. Examples of the most successful thoughts were rather negative including thoughts of exerting an extreme effort, details of friend's death and sadness, hunger and confinement, emotional memories, painful emotional experiences, pain in body parts; however, some of the most successful thoughts were positive including fond and hometown memories, sipping tea, and hearing a pleasant song.

ROI ANALYSIS

Mean percent BOLD signal change during rtfMRI-guided neurofeedback was significantly increased in the functionally localized RIC-ROI at the group ($n = 14$) level during the FB2 training run ($p = 0.014$, **Figure 4A**). Additionally, there was no significant effect for the treatment condition of neurofeedback training (repeated measures ANOVA, $F(2,24) = 2.39$, $p = 0.11$). Using the atlas-defined structural anterior insular cortex ROIs, activation during neurofeedback training was significantly increased bilaterally during the CNTRL (left: $p = 0.033$; right: $p = 0.01$), FB1 (left: $p = 0.034$; right: $p = 0.004$), FB2 (left: $p = 0.004$; right: $p = 0.012$), and FB4 (left: $p = 0.009$; right: $p = 0.02$), training runs (**Figure 4B**). Sub-group analysis of the "best performers" showed significant increases in RIC-ROI during the FB1 ($p = 0.02$) and FB2 ($p = 0.002$) training runs. Sub-group analysis of the "best performances" revealed significant increases during the CNTRL ($p = 0.001$), FB1 ($p = 0.001$), FB2 ($p = 0.004$), FB3 ($p = 0.015$), and FB4 ($p = 0.009$) training runs (**Figure 4C**). No significant increases in RIC-ROI were observed in the final XSFR run for either the "best performers" or the "best performances." Although voxel-wise imaging analysis revealed greater significant cluster sizes in the region of the right compared to left insular cortex, group-level and sub-group ROI analyses showed no lateralization in the insular cortex activations during any of neurofeedback training runs (**Figure 4D**).

The emotional valence of the mental imagery used by subjects was unable to be assessed for 33 of the total of 81 usable neurofeedback runs across subjects due to insufficient detail in the self-reported summaries provided by subjects. Comparing the runs where positive ($n = 24$) and negative ($n = 24$) valence could be ascribed to the type mental strategy employed, no significant difference ($p > 0.05$) was observed between imagery with positive and negative valence in leading to a greater BOLD increase within RIC-ROI (**Figure 5A**). Self-reported mental imagery topics were then grouped into seven major themes with a trend toward significant increases observed for mental strategies involving bad memories and/or pain ($p = 0.052$) and positive thoughts of friends, family, and/or God ($p = 0.058$; **Figure 5B**).

CONNECTIVITY ANALYSIS

Neurofeedback training across FB runs resulted in an increase in functional connectivity between the RIC-ROI and medial frontal gyrus (**Figure 6A**; cluster size = 617, maximum at: −13, 35,

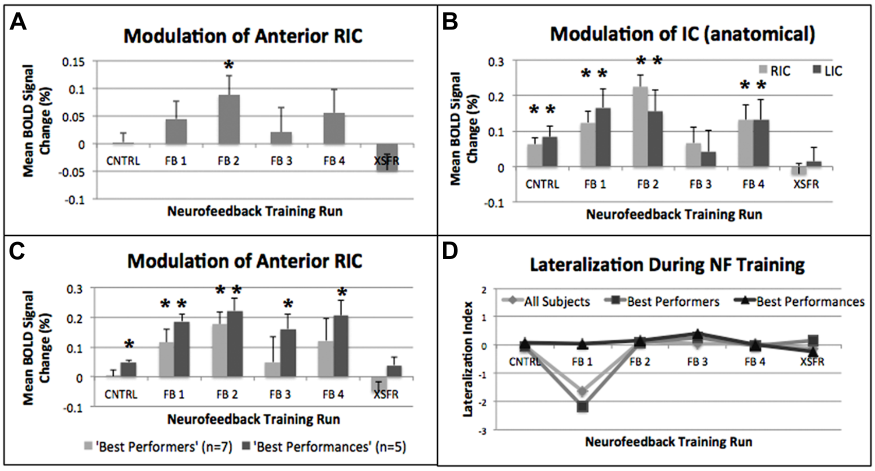

FIGURE 4 | Mean percent BOLD signal changes during each of the neurofeedback training runs showing significant (*$p \leq 0.05$) increases within **(A)** the functionally localized RIC-ROI, **(B)** the structurally defined anatomical right and left anterior insular gyrus (see text), and **(C)** the functionally localized RIC-ROI of the "best performers" ($n = 7$), and the "best performances" ($n = 5$). **(D)** Calculation of a Lateralization Index (see text) using the structurally defined anterior insular gyrus showed no lateralization (+ = right; − = left) when evaluating all subjects, the "best performers," and the "best performances." Error bars shown are standard errors of the mean. RIC, right insular cortex; ROI, region of interest.

40). This cluster of significantly increased connectivity included a small portion of the anterior cingulate cortex. The medial frontal gyrus cluster showed a significant effect for the treatment condition (repeated measures ANOVA, $F(3,27) = 4.83$, $p = 0.010$), with increasing connectivity seen across successive training runs that disappeared for the XSFR run (**Figure 6B**). A significant increase in connectivity between RIC-ROI and the medial frontal gyrus was observed across the neurofeedback training runs with visual feedback (FB4 vs. FB1; $p < 0.0001$), but not between the CNTRL run and XSFR run ($p = 0.56$). There were no significant differences in connectivity detected between the CNTRL and XSFR runs.

DISCUSSION

In this study we aimed to investigate whether healthy controls could learn to modulate brain activity within a functionally localized region of their anterior RIC after a set of brief rtfMRI-based neurofeedback training sessions. At the group-level, increasing brain activity, as measured using the BOLD signal, within the RIC during feedback training was achieved. This is consistent with a number of prior studies suggesting healthy subjects can learn to use neurofeedback to increase BOLD signal in this area during a short training period (Caria et al., 2007, 2010; Johnston et al., 2010; Ruiz et al., 2011; Veit et al., 2012). Participants in our study, however, were only able to increase activity within the functionally localized target RIC-ROI during the second FB training run (FB2). Additionally, participants did not show a training effect over the four training FB runs nor did they show they achieve a learning effect as measured by the XSFR run performed following the neurofeedback training.

The limited ability of subjects to increase activation within the functionally localized RIC could stem from the cross-model nature by which the ROI was localized. Like many other brain regions, the insular cortex consists of a series of its own somatic representations (Baumgärtner et al., 2010; Stephani et al., 2011; Mazzola et al., 2012). Thus, those regions of the insular cortex localized through a motor suppression task may not be able to be modulated through the recall of emotional thoughts. Nevertheless, we observed a significant increase in activity within the target ROI during one of the FB runs. This suggests that insular regions associated with abnormal urges or behavior suppression may be able to be modulated with distinct mental imagery. By expanding on this preliminary work, the therapeutic potential of rtfMRI-based neurofeedback training on conditions with dysfunctional suppression such as Tourette syndrome or obsessive–compulsive disorder could be explored.

Why participants failed to increase activity within the target ROI in training runs following the second FB training run is not known. One possibility is that participants switched to less effective cognitive strategies around the time of this third scanning run. In post-run questioning, only four of the 14 subjects reported using the same thoughts as the prior run so a majority did switch the content of their mental imagery. Another possibility is that there may be some blunting of the brain's emotional circuitry with sustained focus on emotionally relevant thoughts. Arguing against this explanation is our use of a task paradigm that is similar to prior rtfMRI-based neurofeedback studies that did not observe a drop in performance following a third overall training run (Caria et al., 2007, 2010). Other positive neurofeedback studies investigating the ability of subjects to modulate insular activity with emotional imagery, however, did not exceed three neurofeedback runs in a single training session (Johnston et al., 2010; Ruiz et al., 2011; Veit et al., 2012). Further study is needed to determine the ideal number of neurofeedback training runs employing emotional imagery that will optimize operant learning. This knowledge would be a particular asset to fMRI-based neurofeedback studies where scanner time can be expensive and limited.

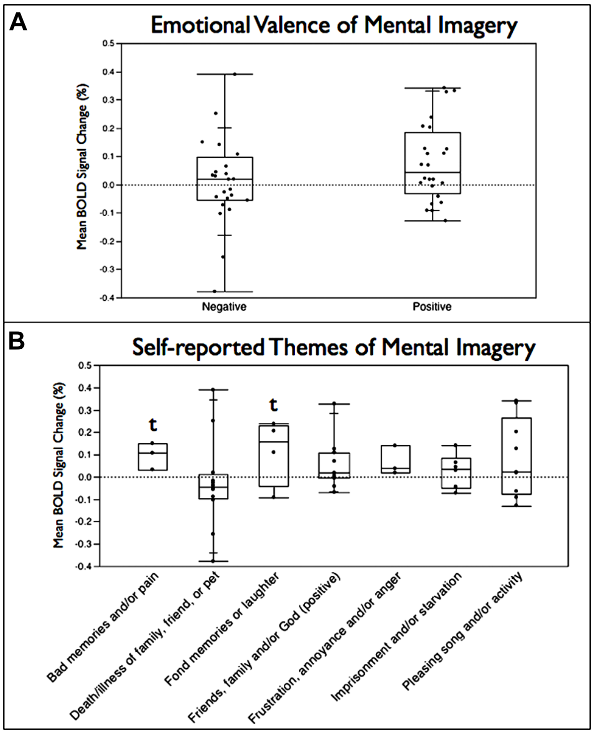

FIGURE 5 | Box plots of mean percent BOLD signal change in the functionally localized anterior RIC-ROI grouped (A) by emotional valence of the mental imagery employed by subjects during the neurofeedback training runs and (B) by major themes for the mental imagery seen. Box is split at the median value and extends one quartile above and below the median; lines extend to maximum and minimum values in the distribution (*t* = statistical trend, $p < 0.06$).

Investigating broader BOLD changes within the RIC using group-level voxel-wise analysis and larger structurally defined ROIs, our study participants demonstrated a broader ability to increase activity during neurofeedback training. There was, however, no rightward lateralization to the insular cortex activations. The lack of lateralization to the anterior RIC may be related to the lack of specific instructions into the valence of the emotional imagery to employ during neurofeedback. Given the evidence supporting an asymmetry in emotional processing within the insular cortex (Craig, 2005), more directed content guidance in terms of the type of emotional imagery to apply during neurofeedback may improve lateralization. In those subjects who provided details of the mental strategies used during neurofeedback runs, however, no significant difference between mental imagery with positive valence and mental imagery with negative valence was found. Additionally, no clearly superior mental strategy emerged after grouping the neurofeedback runs by the overall themes of the mental strategies employed. Although further study may help elucidate the types of mental strategies that are most effective in modulating RIC activity, the therapeutic potential of neurofeedback training involving brain regions associated with emotion processing and regulation may not require unilateral modulation of cortex or modulation of a single limbic region. Rather, it may be more important to induce clinical effects through learned neurophysiological modulation of brain areas that are part of a broader limbic network (Posse et al., 2003; Johnston et al., 2010; Ruiz et al., 2011; Zotev et al., 2011; Linden et al., 2012).

Although participants demonstrated a limited ability in learning how to self-modulate neural activity within their right anterior insular cortex, we did find that the neurofeedback training led to changes in intrinsic brain dynamics. A large cluster of significantly increased functional connectivity between the RIC-ROI and medial frontal gyrus, and to a lesser extent the anterior cingulate cortex, was seen comparing the last training run (FB4) with the first training run (FB1). The medial frontal gyrus is associated with high-level executive functions including monitoring of ongoing actions and performance outcomes, as well as adjusting behavior and learning (Ridderinkhof et al., 2004). Similarly, the anterior cingulate cortex has also been posited to play a role in error monitoring and in making subsequent adjustments in behavior (Kerns et al., 2004). The medial frontal gyrus is also a region considered a key component of the default mode network, which has been hypothesized to be involved self-referential thoughts and autobiographical memory retrieval (Fox and Raichle, 2007; Mason et al., 2007; Buckner et al., 2008). The medial frontal gyrus also

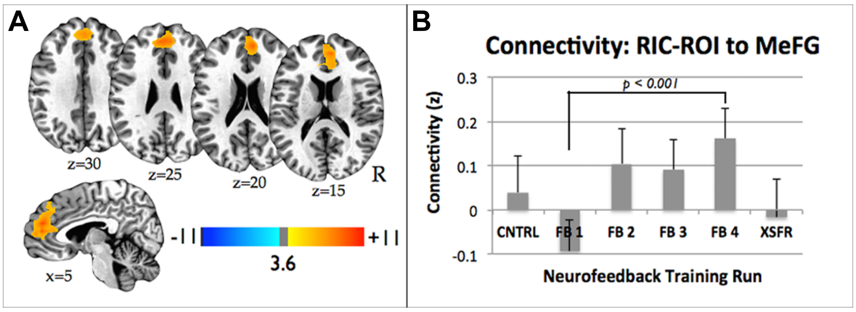

FIGURE 6 | (A) Statistical parametric maps showing significant increase in functional connectivity between the functionally localized anterior RIC-ROI and the rest of the brain from the FB1 to FB4 training run. Images are shown at $p \leq 0.01$, FWE corrected, on axial and sagittal slices of a standard brain in Talairach space. **(B)** Connectivity changes between RIC-ROI and the medial frontal gyrus during each of neurofeedback training runs showing significant increase in connectivity between FB1 and FB4 ($p < 0.0001$). Error bars shown are standard errors of the mean. RIC, right insular cortex; ROI, region of interest.

plays a key role in the "mentalizing network," which partially overlaps with the default mode network and is believed to play a role in the ability to understand and manipulate the mental states of the self and others (Frith and Frith, 2006; Mars et al., 2012). One recent study in which participants were asked to make either reflective "'mentalizing' or 'physical' judgments" about themselves or others found the anterior insula was part of a shared network when we mentalize about our selves or others (Lombardo et al., 2010). Thus, neurofeedback may enable subjects to develop greater volitional control over internal thought processes and in doing so could potentially induce changes in larger brain networks.

Alterations in functional connectivity induced by rtfMRI-based neurofeedback are increasingly being reported. In one study that involved trying to train subjects to modulate activity within their supplementary motor area, decreased connectivity between the supplementary motor area and subcortical regions including the striatum and thalamus was seen (Hampson et al., 2011). Increases in connectivity within frontal and cingulate cortices during neurofeedback of attention-related neuronal activity (Lee et al., 2012) and changes in the speeds of default mode network recovery following neurofeedback training involving the auditory cortex (Van De Ville et al., 2012) have also recently been reported. Furthermore, in a small group of schizophrenia patients, rtfMRI-based neurofeedback training of the insular cortex led to increased connectivity between the insula, medial prefrontal cortex, and amygdala when the best self-regulation training session was compared to the session with the poorest performance (Ruiz et al., 2013). Together with our connectivity results, these preliminary findings support that rtfMRI-based neurofeedback training can lead to changes in brain network connectivity and raises the intriguing possibility that this technique could be used to treat neuropsychiatric disorders known to be associated with network dysfunction (Broyd et al., 2009; Fox and Greicius, 2010; Bullmore and Sporns, 2012).

Following the neurofeedback training paradigm outlined in this study, participants did not demonstrate an ability to increase activity within the insular cortex when the visual neurofeedback signal was withheld. In fact, even by evaluating the best performers and the best performances separately, no significant increases were seen in the final XSFR run, which was designed to detect whether subjects learned how to modulate brain activity in the absence of active feedback. This is in contrast to some prior reports showing healthy subjects were able to retain an improved ability to modulate their brain activity immediately following neurofeedback training (deCharms et al., 2004; Weiskopf et al., 2004; Caria et al., 2007). The majority of rtfMRI-based neurofeedback studies reported to date, however, have lacked an assessment of whether immediately following training participants retain an improved ability to control their own brain activity. It further remains to be demonstrated whether subjects participating in rtfMRI-based neurofeedback experiments learn strategies to self-regulate brain activity that can be repeated outside the scanner environment and ultimately lead to long-lasting cognitive changes (Karbach and Schubert, 2013). Given the inherent limitations of neurofeedback training using fMRI scanners as opposed to more portable and inexpensive options such as EEG-based neurofeedback, this will need to be addressed in future rtfMRI-based studies to help drive this potentially therapeutic tool forward.

In addition to assessing whether study participants learned how to self-modulate brain activity in the insular cortex immediately following neurofeedback training, we tested whether participants were able to increase activity within the insular cortex before any training began. No significant increase in insular cortex activity was detected in our voxel-wise group analysis, but we did detect a significant increase bilaterally in our anatomical insular cortex ROI analysis. It is possible that some individuals may be able to activate their insular cortices through focused emotional imagery even without neurofeedback training. Indeed, the existence of this type of potentially intrinsic human ability has been recently exploited as an approach to testing for cognitive awareness in individuals in a vegetative state (Monti et al., 2010; Yu et al., 2013). While a number of rtfMRI-based neurofeedback investigations have included control arms in which subjects receive sham feedback (deCharms et al., 2005; Caria et al., 2007, 2010; Rota et al., 2008; Yoo et al., 2008), the presence of an inherent capacity of participants to modulate activity within particular brain regions has not been well studied. It is reasonable to propose that the use of sham feedback might actually interfere with an individual's ability to focus their thoughts and could result in an overestimation of the effects of rtfMRI-based neurofeedback training. As such, future neurofeedback studies may benefit from the inclusion of control runs before training.

One limitation to our study, and a shared limitation with most other rtfMRI-based studies, is the limited amount of time during which participants are actually devoting to neurofeedback training. After setup and localization and anatomic scanning, subjects engaged in a total of four training runs, with each run consisting of a total of 2½ min devoted to active regulation training blocks. More effective neurofeedback training may take longer and/or repeated training sessions. Training to modulate brain rhythms with EEG biofeedback may take weeks to see significant effects. In a recent rtfMRI study, schizophrenia patients were trained to modulate brain activity in their bilateral anterior insula cortices using a training paradigm that consisted of three training runs per day for four days spread out over 2 weeks (Ruiz et al., 2011). Despite this more rigorous training paradigm, patients were unable to demonstrate an ability to increase insular activity in the absence of feedback information at the end of the fourth training day. Unfortunately this study did not have a control group so it is unknown if similar findings would be seen in healthy subjects. Our study was also limited by the lack of a control group. Although more important when investigating the clinical effects of neurofeedback as therapeutic intervention, the incorporation of one or more control groups that undergo a similar training regimen while receiving no and sham feedback could help better determine the specific effect providing neurofeedback has on individuals learning to modulate brain activity.

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Brisk heart rate and EEG changes during execution and withholding of cue-paced foot motor imagery

Gert Pfurtscheller[1]*, Teodoro Solis-Escalante[1], Robert J. Barry[2], Daniela S. Klobassa[1], Christa Neuper[1,3] and Gernot R. Müller-Putz[1]

[1] Faculty of Computer Sciences, Laboratory of Brain-Computer Interfaced, Institute for Knowledge Discovery, Graz University of Technology, Graz, Austria
[2] Faculty of Social Sciences, School of Psychology, Brain & Behavior Research Institute, University of Wollongong, Wollongong, Australia
[3] Department of Psychology, Neuropsychology, University of Graz Austria, Graz, Austria

Edited by:
Elisabeth V. C. Friedrich, University of Graz, Austria

Reviewed by:
Pierre Megevand, Hofstra North Shore-LIJ School of Medicine, USA
Jaime A. Pineda, University of California, San Diego, USA

***Correspondence:**
Gert Pfurtscheller, Faculty of Computer Sciences, Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, Inffeldgasse 13/IV, 8010 Graz, Austria
e-mail: pfurtscheller@tugraz.at

Cue-paced motor imagery (MI) is a frequently used mental strategy to realize a Brain-Computer Interface (BCI). Recently it has been reported that two MI tasks can be separated with a high accuracy within the first second after cue presentation onset. To investigate this phenomenon in detail we studied the dynamics of motor cortex beta oscillations in EEG and the changes in heart rate (HR) during visual cue-paced foot MI using a go (execution of imagery) vs. nogo (withholding of imagery) paradigm in 16 healthy subjects. Both execution and withholding of MI resulted in a brisk centrally localized beta event-related desynchronization (ERD) with a maximum at ~400 ms and a concomitant HR deceleration. We found that response patterns within the first second after stimulation differed between conditions. The ERD was significantly larger in go as compared to nogo. In contrast the HR deceleration was somewhat smaller and followed by an acceleration in go as compared to nogo. These findings suggest that the early beta ERD reflects visually induced preparatory activity in motor cortex networks. Both the early beta ERD and the HR deceleration are the result of automatic operating processes that are likely part of the orienting reflex (OR). Of interest, however, is that the preparatory cortical activity is strengthened and the HR modulated already within the first second after stimulation during the execution of MI. The subtraction of the HR time course of the nogo from the go condition revealed a slight HR acceleration in the first seconds most likely due to the increased mental effort associated with the imagery process.

Keywords: motor imagery, beta ERD, HR response, orienting reflex

INTRODUCTION

Cue-paced motor imagery (MI) is one of the most frequently used mental strategies in brain-computer interface (BCI) applications (Pfurtscheller and Neuper, 2001; Wolpaw et al., 2002; Faller et al., 2012) for severely handicapped patients (Neuper et al., 2003; Müller-Putz and Pfurtscheller, 2008; Pichiorri et al., 2011) and rehabilitation after stroke (Birbaumer et al., 2008; Kaiser et al., 2012). The major benefit of such a strategy is that the subject has to pay no attention to any externally presented stimuli during self-paced operation at free will. A prerequisite for a good performance, however, is that the subject experience some cue-paced training sessions without or with feedback. Such training consists of a cue stimulus presentation in slightly varying intervals of a few seconds (Pfurtscheller et al., 2008b; Fazli et al., 2012). The location, color or the form of cue indicates either the type of MI (e.g., right vs. left hand) or whether MI has to be performed or withheld (Solis-Escalante et al., 2012). This procedure results in a number of cortical and subcortical processing steps starting with the stimulus perception and decision making and ending with the requested execution of the MI task, whereby the user focuses attention to visually presented cue stimuli. Recently it has been reported that visually cued imagination of left/right hand revealed the highest classification accuracy ~1 s after cue-onset (Fazli et al., 2012). A similar early classification peak during discrimination between visually cued hand and foot MI was reported by Pfurtscheller et al. (2008b). Remarkable in these studies is not only that the highest classification accuracy was found so early after visual stimulation, but also that this early classification peak was observed in nearly every subject. This stability of the early MI classification within and between subjects is of interest and needs further investigation not only in the cerebral (EEG) but also in the autonomic system (heart rate, HR), because both systems are closely linked together. The first who emphasized the close interaction between brain and heart was Claude Bernard (1867), where he especially pointed to the mutual interaction between the two most important body organs (Darwin, 1872/1999; pp. 71–72). Recently, Thayer and Lane (2009) made an extensive review on the cortical control of cardiac activity and about the pathways by which the prefrontal cortex might influence the control of HR. The prefrontal cortex plays a dominant role in the temporal organization of action (Fuster et al., 2000; Haggard, 2005; Soon et al., 2008) whether physically executed or imagined.

Each externally presented stimulus results in a complex total body response, the orienting reflex (OR), first described by

Pavlov in 1910 (see Pavlov, 1927) and developed in terms of psychophysiological measures by Sokolov (1960). The OR is an organismic reflex resulting in a range of changes (for details see Barry, 2006) such as EEG alpha desynchronization, cephalic vasodilatation, short-lasting HR deceleration and vasoconstriction in the periphery. The basis of this short-lasting HR deceleration over some seconds was identified in the brief prolongation of the cardiac cycle following stimulation reported by Lacey and Lacey (1978, 1980). Barry (1983) noted that the Laceys' vagally-mediated "primary bradycardia" was the beginning of the HR deceleration observed in the OR context, and suggested that this HR deceleration is an obligatory response marking the initial detection of the stimulus onset transient. Another response to external stimuli is the brisk, short-lasting (∼500 ms) beta event-related desynchronization (ERD; Pfurtscheller and Lopes da Silva, 1999) after action-coded visual stimuli - a frequently reported phenomenon (Doyle et al., 2005; Pfurtscheller et al., 2008b; Zhang et al., 2008; Tzagarakis et al., 2010; Wang et al., 2010; Solis-Escalante et al., 2012) related to motor planning, response preparation, response inhibition, and response uncertainty.

The fact that only a minority of people are able to control a BCI properly, without extensive training, depends not only on factors like motivation, mental effort, and mood, but also on automatic operating processes, such as the fast interaction between brain and heart. The aim of this paper is first, to report in detail the brisk reaction of central beta oscillations originating in sensorimotor areas and the HR response after cue-paced movement imagination using a go-nogo paradigm (execution vs. withholding of motor imagery). While the MIgo task was clearly defined, the mental state during the MInogo trials is unknown. Participants were instructed not to move and to relax. Second, this paper aims to discuss how coupled phasic EEG desynchronization and HR deceleration can be interpreted, and provides an understanding of why the classification accuracy in a MI-based BCI can be highest early after the visual cue stimulus. Third, this paper underlines the importance of common EEG and HR changes in BCI research.

MATERIALS AND METHODS

SUBJECTS AND EXPERIMENTAL PARADIGM

The data of 16 healthy subjects (8 males and 8 females, age 23.6 ± 3.5 years) were recorded. Initially 20 subjects participated in this study; the data from four subjects were discarded because of EEG artifacts and recorded muscle contractions in the EMG during MI. All subjects were seated in a comfortable armchair one meter in front of a computer screen. The computer screen showed cues (duration 2 s) for a go (green circle) and nogo experiment (red circle). The interval between the cues was varied between 11 and 14 s.

The experimental paradigm consisted of two runs with cue-paced motor execution (ME) and three runs with cue-paced MI. The data were recorded in two blocks. In the first block, all participants completed two runs of motor execution. Then, after a pause of about 10 min, all participants completed three runs of MI. For the second block, the participants were instructed to perform kinesthetic MI, i.e., to imagine the sensation of moving their legs in response to the cue. Since none of the participants had previous experience with MI, the first experimental block was included to let the participants pay attention to the kinesthetic aspect of the task. Each run consisted of 40 trials with a go/nogo class probability of 50%. The participants' task was to execute or imagine a brisk movement (dorsiflexion) of both feet following a green circle (MEgo, MIgo), or to withhold the motor task (MEnogo, MInogo) if a red circle appeared.

The order of the blocks did not affect the "baseline" activity of the sensorimotor cortex, meaning that motor execution did not pre-activate the cortex, affecting the estimation of relative changes (ERD/ERS). Evidence against a possible effect of the block order comes from an analysis described in Solis-Escalante et al. (2012), in which the baseline activity preceding nogo trials in the conditions ME vs. MI was compared. No statistically significant differences were found. For further details, e.g., the frequency bands under analysis, see Solis-Escalante et al. (2012).

In this work only data from the MI sessions are reported. The protocol was approved by the Ethics committee of the Medical University of Graz and the subjects gave informed written consent before the experiments.

SIGNAL RECORDING

The EEG was recorded with fifteen Ag-AgCl electrodes, arranged in three Laplacian derivations around electrode positions C3, Cz, and C4; overlaying the left hand, foot, and right hand sensorimotor cortex. Inter-electrode distance was 2.5 cm. Reference and ground electrodes were attached to the left and right mastoid, respectively. In addition to the EEG, the EMG was recorded from the tibialis anterior muscles in both legs using bipolar derivations. The ground electrode for EMG was attached to the right hip. The EMG was pre-processed before recording. Raw EMG signals were band-pass filtered between 1–1000 Hz, baseline-corrected, full-wave rectified, and integrated with a time constant of 100 ms. EEG and the integrated EMG were recorded with a biosignal amplifier (g.BSamp, Guger Technologies, Austria). Sampling rate was 250 Hz, with filters set between 0.5 and 100 Hz, and a notch filter (50 Hz), for both EEG and integrated EMG. The electrocardiogram (ECG) was recorded from a single bipolar derivation. The negative lead was attached to the chest at the left (mid) clavicular line and the 2nd intercostal space, and the positive lead was attached to the chest at the left midaxilar line and the 6th intercostal space. The ground electrode was placed on the right hip. Self-adhesive Ag-AgCl electrodes were used for these recordings. ECG was recorded with a band-pass filter between 2 and 100 Hz and also sampled at 250 Hz.

EEG PROCESSING

The monopolar EEG data recorded with respect to the left mastoid were transformed with a Laplacian filter to improve the SNR of the signal. The inter-trial variance method (Pfurtscheller and Lopes da Silva, 1999) was used for quantification of the event-related (de)synchronization (ERD/ERS). Time-frequency representations were calculated to visualize the ERD/ERS patterns;

only significant ERD/ERS values are displayed (Graimann et al., 2002). ERD/ERS quantification and visualization was managed by the BioSig toolbox (Schlögl and Brunner, 2008; available online http://biosig.sourceforge.net/).

The data were analyzed between 8 and 45 Hz in intervals of 2 Hz. Trials were filtered with a 5th order Butterworth filter, and the ensemble average was subtracted from individual trials. This operation reduces the contribution of phase-locked responses to the ERD/ERS quantification (Kalcher and Pfurtscheller, 1995). The trials were squared and averaged. A moving average window of 250 ms smoothed the ERD/ERS estimation. Significance intervals ($p = 0.05$) were computed with a Box-Cox transformation (Box and Cox, 1964). The reference interval for the relative power changes was 2–4 s prior to cue-onset. For the determination of the most reactive subject-specific beta bands we used the ERD/ERS maps computed from the motor execution task (MEgo) and the discriminability (Cohen's kappa) calculation (Cohen, 1960) between the beta rebound and the reference interval. The beta rebound is much larger during physical execution of movement compared to imagination of the same movement (Solis-Escalante et al., 2012). Hence, to obtain a reliable estimation of the beta band, we used the MEgo trials instead of the MIgo trials. User-specific bands were defined according to the strongest ERS response following the movement execution in MEgo trials. Details on selection of a user-specific band are given elsewhere (Solis-Escalante et al., 2012).

CALCULATION OF THE HEART RATE (HR) CHANGES

The first step in ECG processing is to detect the QRS complexes in the ECG signal. The interval between consecutive QRS-complexes marks the time from one heart contraction to the next (RR interval; RRI). The QRS-complex was detected automatically based on an algorithm using a filter bank to decompose the ECG signal into various sub-bands (Afonso et al., 1999; implemented in the Biosig toolbox). After detecting every QRS-complex, the RRI is estimated from every pair of successive complexes. The HR value during an RRI equals the inverse of the RRI concerned, and (in beats per minute) is linearly interpolated between two complexes; the resultant time series is averaged across trials from the same class. To obtain HR changes the individual HR signals were synchronously averaged relative to cue-onset (Pfurtscheller et al., 2007).

ARTIFACT REJECTION

Trials were rejected if the EMG from the left or right leg exceeded a threshold. For MInogo trials, this threshold was equal to the mean plus three times the standard deviation of the EMG at rest. For MIgo trials, the threshold was equal to the mean plus five times the standard deviation of the EMG at rest, since imagined movements can increase the tonus of the target muscles (Guillot et al., 2007). The "EMG at rest" period was defined as a 5 s interval before cue onset.

After computing the HR, additional trials were rejected by identification of extreme HR changes, i.e., outliers. The first derivative of the HR from each trial was computed, and the absolute value was analyzed using descriptive statistics. Trials were rejected in an iterative fashion: (i) compute the first and third quartile and the interquartile distance from all trials available (class-wise, e.g., separately for MIgo and MInogo); (ii) reject trials if any value of the HR's first derivative was: (1) less than the first quartile minus 1.5 times the interquartile distance, or (2) greater than the third quartile plus 1.5 times the interquartile distance; (iii) repeat until all outliers have been removed.

STATISTICAL ANALYSIS

The statistical significance of EEG band power changes (ERD, ERS) and HR changes was evaluated with a t-percentile bootstrap algorithm, using the implementation of the BioSig toolbox. Upper and lower confidence intervals were obtained from 500 resample repetitions, at confidence levels of 0.05 and 0.01.

Statistical analysis comprised a paired *t*-test for evaluating differences in beta ERD and HR between MIgo and MInogo and a Pearson's product moment correlation for evaluating possible relations between beta ERD and HR deceleration. Comparisons between MIgo and MInogo were analyzed for significant differences with a t-percentile bootstrap algorithm (as described above) for every sample in the time series.

RESULTS

EEG TIME-FREQUENCY MAPS DURING go AND nogo CONDITIONS

To obtain an overview of the dynamics of sensorimotor rhythms in the go (MI) and nogo condition (withholding of MI), time-frequency maps were calculated separately for each condition. Examples from three characteristic subjects (A–C) are shown in **Figure 1**. The maps in **Figures 1A,B** (left panels) display the classical response in the beta band during imagined dorsiflexions of both feet (MIgo) namely a long-lasting (~1–2 s), midcentrally localized, peri-imagery ERD during execution of the imagery process and a post-imagery ERS (beta rebound) after termination of this process. But subjects can also show an early beta ERD without following beta ERS during MIgo (example see **Figure 1C**, left panel), similar to the early ERD in the nogo condition (**Figures 1A–C**, right panels). Because of the variable duration of each imagery task and the alignment of the averaging process to cue-onset and not to the exact end of MI, the beta ERS (beta power increase) in the go condition is relatively long-lasting. In the nogo condition (**Figure 1** right panels) the early beta ERD starts immediately after cue-onset, has a duration of ~500 ms and is terminated by a brisk beta ERS with a maximum ~1 s after cue-onset (panels A–C).

The subject-specific beta band (mean ± *SD*) determined from the time-frequency maps and used for further analyses was between 18.8 ± 4.7 and 28.4 ± 4.8 Hz. The magnitudes and latencies of beta power minima (largest ERD magnitude) and HR minima measured within the first second after stimulation onset are summarized in **Table 1** for both the go and nogo conditions.

The beta ERD was significantly (paired *t*-test) larger (39.82 vs. 32.00%; $t = 5.37$, $p < 0.001$) during MIgo compared to MInogo, but its peak latency was not significantly longer (471 vs. 397 ms; $t = 1.05$, ns). In contrast, HR deceleration was somewhat smaller in MIgo vs. MInogo (1.00 vs. 1.94 %, $t = 2.03$, $p = 0.06$); again, peak latencies (640 vs. 652 ms) did not differ significantly ($t = 0.18$, ns).

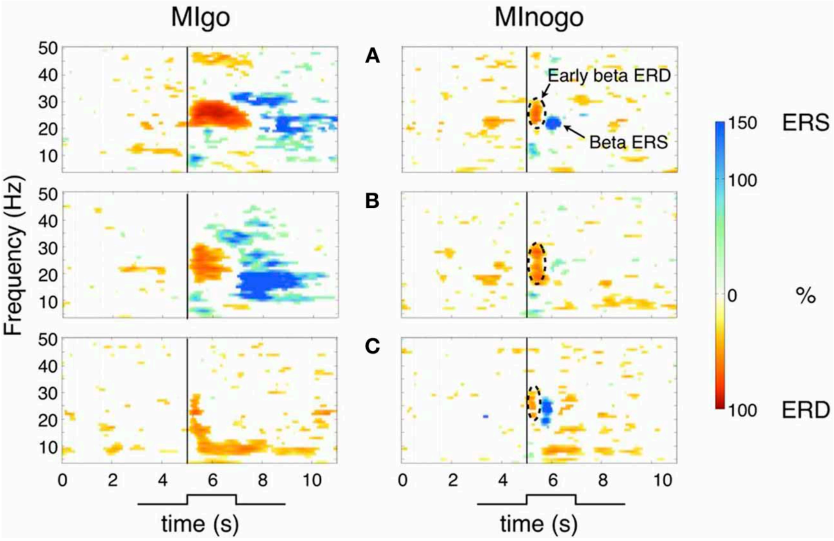

FIGURE 1 | Time-frequency maps for MIgo and MInogo from three characteristic subjects (A–C) illustrating different reactivity patterns during execution and withholding of MI. Common for all three subjects is only the early beta ERD during MInogo (marked by stippled circles). Significant ERD values are displayed in "red" and significant ERS values in "blue." The vertical line at second 5 indicates cue-onset. **(A)** Early beta ERD and beta ERS during MIgo and MInogo. **(B)** Early beta ERD and beta ERS during MIgo, and early ERD and weak beta ERS during MInogo. **(C)** Early beta ERD during MIgo and early beta ERD with beta ERS during MInogo.

Table 1 | Mean ± *SD* (16 subjects) for latency (ms) and magnitude (%) of early beta power minimum (beta ERD) and change of HR for go and no conditions.

	ERD				HR			
	Latency (ms)		Amplitude (%)		Latency (ms)		Amplitude (%)	
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***
MI go	471	211	−39.82*	20.56	640	224	−1.00	1.84
MI nogo	397	139	−32.00*	23.78	652	276	−1.94*	1.28

indicate statistical significance ($p < 0.01$, see **Figure 2).*

CHANGES OF BETA POWER AND HR DURING EXECUTION (go) AND WITHHOLDING (nogo) OF MOTOR IMAGERY

Grand averages of changes in percentage HR (upper panels) and EEG beta power (lower panels) for both conditions are displayed in **Figure 2**. Reference interval is 2–4 s before cue presentation. Beside the mean ± SE also significant changes (bootstrap $p = 0.01$) are indicated. Excepting the HR changes in the go condition, all other HR and EEG changes (HR deceleration and EEG beta desynchronization) were significant in the first second after cue presentation in go and nogo conditions ($p < 0.01$). While in the go condition the HR showed a significant ($p < 0.01$) acceleration after the brisk deceleration, no further significant HR changes were observed after the deceleration in the nogo condition.

For a direct comparison of the beta power decrease during motor planning in the go/nogo conditions after visual cue presentation with a similar 248-channel MEG study (Tzagarakis et al., 2010) the reference interval was changed to 0–1 s prior to cue onset [the standard reference interval for the processing of all EEG and HR data (**Figure 2**) was 2–4 s prior to cue onset in accordance with the work of Solis-Escalante et al. (2012)]. Common for both studies (**Figures 3A,B**) is the early beta power decrease from cue onset (Tzagarakis et al., 2010 reported a delay of 120 ms) not dependent on the type of information provided by the visual stimulus but rather determined by a constant visuomotor delay. The different behavior of the beta ERD between execution and withholding of MI starts between 200 and 300 ms after cue onset, indicating on the one hand that the cue stimulus-induced early beta ERD peaks at ~400 ms, and on the other hand that the cognitive task (execution of MI) is able to modulate this desychronization.

When searching for possible interpretations of the HR responses in the go and nogo condition we subtracted the nogo HR response from the go response (MIgo minus MInogo) and achieved a new response pattern termed "hypothetical" HR response (**Figure 4A**) with a HR acceleration starting immediately at cue onset and a maximum at ~2 s latter. Remarkable is the similarity between the "hypothetical" HR response in **Figure 4A** and the HR responses in a similar no/go study without any motor preparation displayed in **Figure 4B** (Lawrence and Barry, 2010). The brisk HR deceleration is the dominant feature in both studies.

INTERDEPENDENCY BETWEEN EARLY ERD AND BRISK HR DECELERATION

When testing linear inter-subject correlations between beta ERD and HR deceleration within the first second after cue-onset, no significant correlation was found for MInogo (Pearson correlation coefficient $r = 0.05$, $p = 0.86$; see **Figure 5B**); the correlation for MIgo was in the expected direction (greater deceleration with greater ERD) but failed to reach significance ($r = -0.28$, $p = 0.29$; see **Figure 5A**).

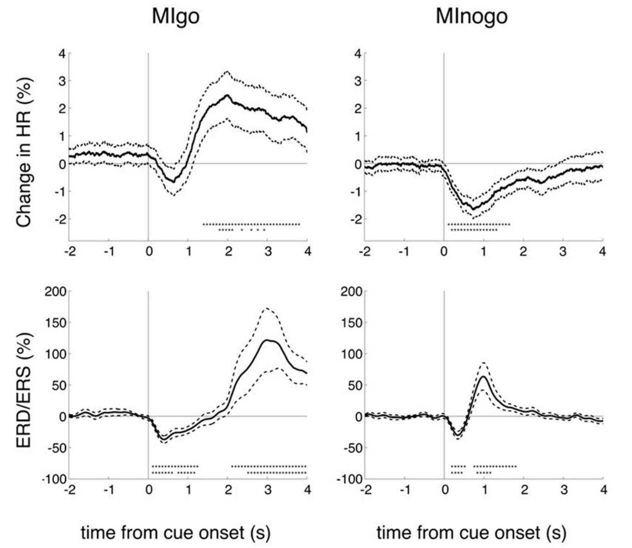

FIGURE 2 | Grand averages of percentage HR and beta power (ERD/ERS) changes for execution (MIgo) and withholding (MInogo) of foot motor imagery. In addition to the mean and the standard error (stippled lines) also the significant changes (bootstrap) are displayed (one asterisk vertically $p < 0.05$, and two asterisks vertically $p < 0.01$). Data of 16 subjects. Note the significant HR decrease in the nogo condition and the significant early beta ERD in both the go and nogo conditions.

DISCUSSION

The following findings need special attention: (i) the slightly different reactivity patterns in the EEG during go and nogo conditions within the first second in the form of an early beta ERD, (ii) the different magnitudes of brisk HR decelerations in both conditions and (iii) that no significant correlation was found between early ERD and HR deceleration.

EEG CHANGES DURING EXECUTION (go) AND WITHHOLDING (nogo) OF MI

In the EEG rhythms, various phenomena have to be differentiated during execution and withholding of MI. First the early beta ERD with a peak ∼400 ms after cue-onset observed in both conditions, second the longer-lasting beta ERD associated with the conscious intention of MI (peri-imagery ERD) in the go condition, and third the beta rebound (post-imagery ERS) terminating the beta ERD. In the go condition the peri-imagery ERD becomes either superimposed on the early beta ERD within the first second (see **Figures 1A,B**) or the early beta ERD remains in the go condition (**Figure 1C**). Whether the absence of a longer-lasting beta ERD acts as indicator for a not correctly performed imagery task can only be speculated. The ERD represents a process to enable focal attention so that information processing may be optimized (Lopes da Silva, 1991) or, in other words, the ERD indicates a state of cortical activation (Gerloff et al., 1998; Pfurtscheller and Lopes da Silva, 1999; Leocani et al., 2001; Doyle et al., 2005). The beta ERS corresponds to a state of deactivation of the motor cortex circuitry and signifies active immobilization (Salmelin et al., 1995). In the nogo condition the beta ERD begins to recover 400 ms after cue onset and reaches its peak ERS at 1000 ms (see **Figure 2** right lower panel and **Figures 1A,C**). Support for an activation of the foot representation area during MIgo came from fMRI studies. Physical execution but also mental simulation of foot/toe movement is not only accompanied by peri-imagery and mid-centrally localized beta ERD (Pfurtscheller et al., 2006a) but also by a positive fMRI BOLD signal localized to the foot representation area (Ehrsson et al., 2003).

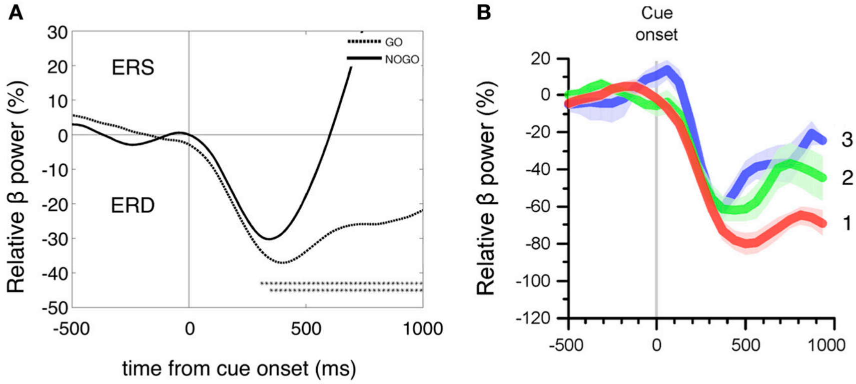

FIGURE 3 | (A) Details of the grand average beta power time courses (ERD/ERS) of 16 subjects within the first second after cue onset for MIgo (dashed line) and MInogo (continuous line). Beta power was compared between MI go and MInogo (bootstrap, one asterisk $p < 0.05$, two asterisks $p < 0.01$) and revealed significant differences starting at 250 ms after cue onset. **(B)** Time courses of relative beta power changes after a visually instructed reaching task with one, two, or three possible target directions (with permission modified from Tzagarakis et al., 2010). Note the similar early beta ERD with a maximal magnitude at ∼400 ms in EEG **(A)** and MEG **(B)** recordings during different motor tasks.

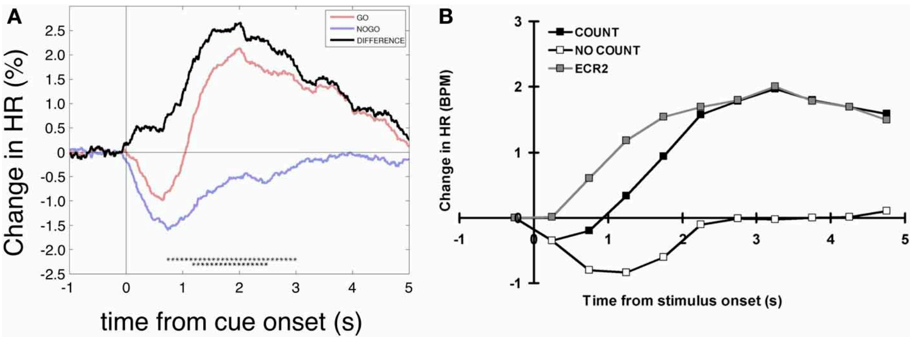

FIGURE 4 | Heart rate changes after go and nogo cues. (A) Grand average time courses of percentage HR changes aligned to cue onset referenced to an interval 1–0 s prior to cue onset (different from the text and analyses above). Displayed are the HR responses for MIgo, MInogo and their difference (hypothetical HR acceleration). Significant differences between conditions are marked with black asterisks (bootstrap, one asterisk $p < 0.05$, two asterisks $p < 0.01$). **(B)** Grand average HR response for silent counting of tones (COUNT) vs. no-count (NO COUNT) and hypothetical HR response (DIFFERENCE). Modified from Lawrence and Barry (2010).

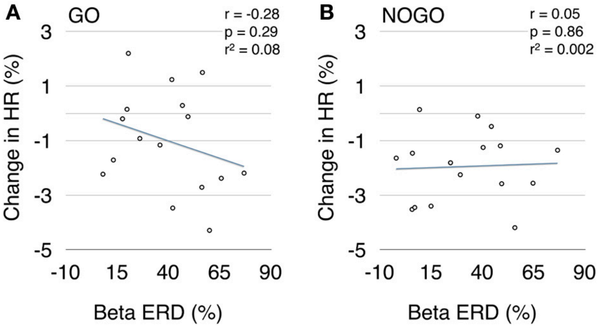

FIGURE 5 | Scatter plot between early beta ERD (%) and brisk HR decrease (%) during motor imagery (A) and withholding of motor imagery (B).

In respect to the early ERD direct recordings from single neurons of the monkey‘s motor cortex are of interest. Such neurons start to discharge 60–80 ms after occurrence of a visual cue, indicating the direction of the upcoming movement (Georgopoulos et al., 1982). Preparatory changes in neuronal activity prior to movement execution have been documented also in monkey premotor and primary cortex 100 ms after the visual cue signal (Riehle and Requin, 1995). These studies show clearly that the motor cortex is engaged as early as about 100 ms after an informative visual cue indicates to execute or withhold a specific motor task. Similarly, in another monkey study, the beta activity displayed an early ERD in go and nogo conditions starting ~110 ms after visual stimulus presentation (Zhang et al., 2008). Therefore, we can conclude that the early phasic beta ERD observed in our data is a sign of preparatory activity in motor cortex networks triggered by the visual stimulus and modulated by the cognitive task.

Most interesting is that the early beta ERD displays a slightly but significant stronger magnitude ($p < 0.01$) and longer peak latency (n.s.) during MIgo than in MInogo (**Table 1** and **Figure 3A**). The decision to execute or withhold MI is estimated to occur ~190 ms after stimulation (Zhang et al., 2008). Support for such an early stimulus induced preparatory activity in motor cortex networks came from two MEG studies (Tzagarakis et al., 2010; Wang et al., 2010). In Wang's study subjects were asked to imagine four different center-out movements using the wrist after visual target onset. The source-space multivariate test revealed that by 300–400 ms after target onset the cortical activity becomes highly modulated and can be used to decode the type of covert movement. Tzagarakis et al. reported on a 248-channel whole head MEG study while subjects performed a visually instructed reaching task with one, two, or three possible directions. The early beta ERD with a maximum at ~400 ms is heightened with decreased directional uncertainty (see **Figure 3B**). Remarkable is that the early beta ERD displays a peak at 500 ms in such two completely different studies, one with MEG and response uncertainty and the other with EEG and MI. This suggests that the early beta ERD can be maximal around 500 ms after cue onset not only in EEG and MEG recordings, but also can be modulated by different cognitive processes such as MI or response uncertainty.

HR CHANGES DURING EXECUTION (go) AND WITHHOLDING (nogo) OF MI

The initial obligatory post-stimulus HR deceleration in the OR context mentioned in the Introduction is exemplified in response to the nogo cue, as illustrated in the right panel of **Figure 2**. This brisk HR response is significantly and clearly of larger magnitude when compared with the response during MI (go condition; **Figure 2** left). Of interest is that this HR response is nearly identical with the "hypothetical" HR response difference in a similar go-nogo experiment where subjects were required to silently count the number of tones (go condition); in the nogo condition the subjects were told to relax during tone presentation (Lawrence and Barry, 2010; see also **Figure 4B**). These authors linked their hypothetical HR acceleration to the increased mental effort of the count condition. The hypothetical HR acceleration during MI is linked to the mental effort in the same fashion. A HR acceleration is characteristic for an increased mental effort during the simulation of a motor act (MI) (Decety et al., 1991; Oishi et al., 2000; Pfurtscheller et al., 2006b, 2008a).

COUPLING BETWEEN EARLY BETA ERD AND BRISK HR DECELERATION

The beta ERD and concomitant HR deceleration after stimulation is not an isolated phenomenon but is also found during preparation for movement or even in the resting brain. The pre-movement beta ERD and the pre-movement HR deceleration are well documented phenomena (Damen and Brunia, 1987; Papakostopoulos et al., 1990; Florian et al., 1998; Pfurtscheller and Lopes da Silva, 1999). A slow cyclic (in intervals of ∼10 s) central beta (alpha) power decrease and a nearly simultaneous HR decrease (beat-to-beat increase) in the resting state was reported recently (Pfurtscheller et al., 2012a,b). If the desynchronization of sensorimotor rhythms prior to movement can be interpreted as a correlate of preparatory activity then also the early beta ERD after cue presentation can be seen as stimulus triggered preparatory activity in the sensorimotor system. This preparatory activity, and also the HR deceleration, very likely result from routine processes operating automatically and unconsciously (Koch, 2003; Haggard, 2005). The EEG-HR coupling prior to voluntary movement, during rest and after visual stimulation can be seen as an example of the fast interaction between brain and heart mediated by pathways most likely from the prefrontal cortex to cardiovascular nuclei in the brain stem and vagally via the sino-atrial (SA) node to the heart (Thayer and Lane, 2009). The SA node responds very quickly to vagal (∼150 ms latency) in contrast to sympathetic (∼1–2 s) influences (Smyth et al., 1969).

Visual information is not only mediated by the lateral geniculate body, but also by the superior colliculus. The superior colliculus is important for the control of saccadic eye movements (Krauzlis et al., 2004), and is believed to be responsible for a transient increase in blood pressure and HR by drive of sympathetic activity (Iigaya et al., 2012) Electrical stimulation of the optic tract also increases blood pressure and HR, and inhibits baroreflex vagal bradycardia, mediated by the superior colliculus (Cheng et al., 2001). The participation of the superior colliculus in reflexive vagal mediated primary bradycardia (Lacey and Lacey, 1980; Barry, 1986) is therefore very unlikely.

That no significant correlation was found between early beta ERD and HR deceleration during MIgo (see **Figure 5A**) might be explained by different reasons. While the MIgo cardiac response can be conceptualized as an additional cardiac acceleration reflecting mental effort, superimposed on the reflex bradycardia triggered by the cue (see **Figure 4A**), a comparative examination of the corresponding beta power response profiles gives a more complex picture (see **Figure 3A**). Here the reflexive early beta ERD (peaking at ∼400 ms) is superimposed on the peri-imagery beta ERD induced by the conscious mental simulation of foot movement. Although the early beta ERD with the following beta ERS in the nogo condition is an automatically induced response, only the early beta ERD can be considered as a component of the OR. The relationship between these differences in the EEG and HR response profiles during MIgo is complex and needs further exploration, possibly going beyond the linear correlation of responses in the short interval tested here. Another reason for the non-significant correlation could be that in all subjects the EEG was recorded at the vertex only (Cz: Laplacian derivation) although it is known from multichannel MEG recordings that the source of the beta band ERD can vary in the peri-Rolandic region across subjects (Tzagarakis et al., 2010). Beside the EEG also the ECG can induce some variability. The HR displays two preferential rhythms, one around 0.25 Hz (respiration) and one around 0.1 Hz (blood pressure or Mayer waves) (De Boer et al., 1985) as well as fluctuations induced by "central commands" (see review Benarroch, 1993; Thayer and Lane, 2009). Slow intrinsic HR fluctuations during rest can be as high as ∼10 % of the mean HR (Pfurtscheller et al., 2012a) and mask the relatively small (∼2%) brisk HR deceleration induced after stimulation.

CONCLUSION

The early beta ERD with the largest magnitude at ∼400 ms is slightly, but significantly ($p < 0.01$) larger during execution (go) as compared to withholding of MI (nogo). At the same time the HR displays a significant ($p < 0.01$) brisk deceleration only during withholding of MI. Both the early beta ERD and the HR deceleration are the result of an automatic operating process and probably part of the OR (Barry, 2006). Of interest, however, is that both automatic reactions in brain and heart can be modulated by the increased mental effort associated with execution of MI. The calculation of the "hypothetical" HR acceleration introduced by Barry (1984) offers a new way to explore the mental effort during motor imagery early after stimulation. A high mental effort during imagined movements is accompanied by a HR increase (Decety et al., 1991; Oishi et al., 2000). Such indicator of mental effort could be used in a BCI to improve its performance (Pfurtscheller et al., 2010). For online monitoring of the mental effort in a cue-paced MI task, the averaged HR response of the MInogo condition obtained in a pre-experiment has to be subtracted from each ongoing HR response (calculation of the "hypothetical" HR). By this way the mental effort can be supervised and an intervention made if necessary.

The early beta ERD is an important brain feature that might be responsible for the early classification peak in imagery-based BCIs because of its somatotopic organization as demonstrated recently (Pfurtscheller et al., 2008b). The close relationship between early ERD and action-coded visual stimulation also was discussed elsewhere (Waldert et al., 2008; Wang et al., 2010). If the visual stimulus indicates only one specific type of MI the attention is focused on this specific imagery task and results in an early beta ERD in both conditions (go/nogo). The results suggest that the early classification peak in cue-paced BCIs is very likely the result of an automatic operating process induced by the preparatory visual cue stimulus. This hypothesis, however, needs to be further tested, possibly with an auditory cue stimulus.

The fast interaction between brain and heart is a basic factor in BCI research. HR slowing and concomitant pericentral EEG desynchronization is not only characteristic for the planning and/or preparation of a motor task (e.g., ME or MI), but also a dominant feature immediately after visual cue presentation. Still open for research and discussion is the link between slow (∼0.1 Hz) spontaneous HR and EEG oscillations during awake rest (Pfurtscheller et al., 2012a,b). In this respect, the finding that the relation between early beta ERD and brisk HR deceleration is very likely the result of an automatic process, operating after visual cue presentation, is a small step to improve the success rate in BCI research and focus research attention on the importance of intrinsic HR and blood pressure oscillations at a frequency of around 0.1 Hz.

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Prediction of brain-computer interface aptitude from individual brain structure

S. Halder[1,2,3]*†, B. Varkuti[1†], M. Bogdan[3,4], A. Kübler[1], W. Rosenstiel[3], R. Sitaram[5] and N. Birbaumer[2,6]

[1] *Department of Psychology I, University of Würzburg, Würzburg, Germany*
[2] *Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany*
[3] *Wilhelm-Schickard Institute for Computer Science, University of Tübingen, Tübingen, Germany*
[4] *Department of Computer Engineering, University of Leipzig, Leipzig, Germany*
[5] *Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA*
[6] *Ospedale San Camillo, Laboratorio di Neuroscience Comportamentale, Istituto di Ricovero e Cura a Carattere Scientifico, Venezia, Italy*

Edited by:
Cuntai Guan, Institute for Infocomm Research, Singapore

Reviewed by:
Clemens Brunner, Graz University of Technology, Austria
Michal Lavidor, Bar Ilan University, Israel

****Correspondence:***
S. Halder, Department of Psychology I, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany.
e-mail: sebastian.halder@uni-wuerzburg.de

†These authors have contributed equally to this work.

Objective: Brain-computer interface (BCI) provide a non-muscular communication channel for patients with impairments of the motor system. A significant number of BCI users is unable to obtain voluntary control of a BCI-system in proper time. This makes methods that can be used to determine the aptitude of a user necessary.

Methods: We hypothesized that integrity and connectivity of involved white matter connections may serve as a predictor of individual BCI-performance. Therefore, we analyzed structural data from anatomical scans and DTI of motor imagery BCI-users differentiated into high and low BCI-aptitude groups based on their overall performance.

Results: Using a machine learning classification method we identified discriminating structural brain trait features and correlated the best features with a continuous measure of individual BCI-performance. Prediction of the aptitude group of each participant was possible with near perfect accuracy (one error).

Conclusions: Tissue volumetric analysis yielded only poor classification results. In contrast, the structural integrity and myelination quality of deep white matter structures such as the Corpus Callosum, Cingulum, and Superior Fronto-Occipital Fascicle were positively correlated with individual BCI-performance.

Significance: This confirms that structural brain traits contribute to individual performance in BCI use.

Keywords: BCI, motor imagery, aptitude, DTI, fractional anisotropy

1. INTRODUCTION

Brain-computer interface (BCI) provide a non-muscular control channel that can be used for communication, device control, or rehabilitation. Most non-invasive BCI rely on control signals that are extracted from components of the electroencephalogram (EEG), first described by Berger (1929), that can be voluntarily modulated. One of the earliest control signals used successfully for communication with severely paralyzed amyotrophic lateral sclerosis (ALS) patients were slow cortical potential (SCP) (Birbaumer et al., 1990, 1999). Later studies were often based on event-related potential (ERP), mainly the P300, [(Farwell and Donchin, 1988; Polich, 2007; Nijboer et al., 2008b; Silvoni et al., 2009; Lulé et al., 2013); see Kleih et al. (2011) for a review]. P300 BCI have the advantage of requiring almost no user training. Steady state-evoked potential (SSEP) share this advantage and have also been successfully used for BCI (Regan, 1977; Middendorf et al., 2000; Allison et al., 2008). It is also possible to control a BCI by performing motor imagery of different body parts such as hands or feet which causes event-related desynchronization (ERD) and event-related synchronization (ERS) of the sensorimotor rhythm (SMR) (also referred to as μ-rhythm) (Pfurtscheller and da Silva, 1999; Neuper et al., 2003; Kübler et al., 2005). Novel approach utilize the principles of semantic classical conditioning to establish a communication channel (Furdea et al., 2012; De Massari et al., 2013; Ruf et al., 2013).

In the context of this study BCI paradigms that rely on user training are of particular interest. This includes BCI based on the modulation of SMR or SCP. Of these we will focus on BCI based on the modulation of the SMR using motor imagery. The SMR is a brain rhythm in the frequency range of 8–15 Hz which is insensitive to visual input (Kuhlman, 1978). Distinct rhythms originating from the somatosensory cortex are modulated by executed movement or movement imagery depending on the body part involved in the task (Hari and Salmelin, 1997; Pfurtscheller et al., 1997). In addition to modulation in the alpha band, modulation can also occur in a second peak in the beta band (16–30 Hz). This peak is located anteriorly to the sources of the alpha component of the SMR (Hari and Salmelin, 1997).

Two approaches to achieving high accuracies with SMR bases BCI have been established. Studies more focused on single sessions with high information transfer rate (ITR) with healthy participants use a large number of EEG sensors to which advanced spatial filtering methods such as common spatial patterns (CSP) are applied (Ramoser et al., 2000; Blankertz et al., 2008). This requires fewer sessions of user training. In studies focused on BCI usage with patients multiple sessions should be possible with a minimum preparatory overhead (such as applying a large number of sensors) which is why user training enabling BCI usage with a low number of sensors is the preferred approach (Neuper et al., 2003, 2009; Kübler et al., 2005; Nijboer et al., 2008a). The time of training is one the reasons for the need of a reliable predictor that estimates the aptitude of a potential user to control such a BCI before training. Additionally, current research on the use of EEG-based BCI suggests that a certain percentage of users would not at all be able to gain sufficient voluntary control of an EEG-BCI within an acceptable timeframe: a phenomenon recently referred to as BCI inefficiency (Kübler et al., 2011). The criterion level of free control is defined to be at 70% selection accuracy Kübler et al. (2001, 2004). In Guger et al. (2009) 50% of participants ($N = 99$) did not achieve accuracies above 70% with an SMR based BCI, in Hammer et al. (2012) 37.5% of participants ($N = 80$) failed to achieve accuracies above 70%. The availability of reliable performance prediction methods would also considerably improve the process of selecting the most promising paradigm for a particular user. Additionally, training programs could be adapted to the aptitude of a particular user at a much earlier stage. Considering that BCI are primarily intended for patients who are diagnosed with severe diseases that not only lead to motor impairment but also to a reduced attention span it would be advantageous to be able to quickly choose a suitable BCI and training strategy that best fits the patients needs (Birbaumer et al., 2008). It was shown that the amplitude of the SMR during rest strongly predicts the performance of a participant in a subsequent SMR-BCI session (Blankertz et al., 2010). A study using functional magnetic resonance imaging (fMRI) has shown that there is a strong difference in supplementary motor area (SMA) activation between high and low aptitude SMR-BCI users when performing motor imagery (Halder et al., 2011). This difference is enhanced when the participants observe motor tasks. For P300- based BCI it could be shown that prediction is possible using data collected from auditory oddball ERP recorded before the experiment but also using features extracted during stimulation (Mak et al., 2012; Halder et al., 2013).

In the light of recent studies on the association of bundle specific white matter integrity and EEG features in healthy subjects (Valdés-Hernández et al., 2010), the link of interhemispheric white matter connectivity with EEG frontal coherence (Teipel et al., 2009) and the relation of interhemispheric transfer time to DTI derived measures of white matter integrity, it is apparent that the conduction properties (e.g., conduction velocity, myelinization, and local fiber density) of the brain are determined by the underlying white matter network and that these properties might in turn significantly influence EEG features on both the trait and state level. Specifically, the dynamics of the resting state alpha rhythm appear to be connected to white matter architecture (Valdés-Hernández et al., 2010). Due to the dependence of the resting state SMR that was shown in Blankertz et al. (2010) and the reported link between EEG features in that frequency range and white matter architecture (Valdés-Hernández et al., 2010), we assumed that there may be a link between white matter architecture and SMR-BCI aptitude.

Based on these findings we hypothesized, that structural characteristics of the user such as head size, white matter integrity, or cortical surface area also influence BCI aptitude. We hypothesized that structural differences in the brains of high and low aptitude users can be identified and that these features not only differ between the groups of high and low aptitude users, but are strongly correlated with individual BCI aptitude. In order to investigate this relationship we conducted a single EEG-BCI session and a structural MRI measurement with 20 healthy participants. We refer to the potential skill of BCI usage of an individual as aptitude. The performance achieved by naive BCI users has been shown to be predictive of subsequent peformance in previous studies (Neumann and Birbaumer, 2003; Kübler et al., 2004). Thus, aptitude is used a synonym for the performance in the first BCI session in the context of this paper.

2. METHODS

2.1. PARTICIPANTS

Twenty healthy participants (7 female, mean age 24.5 years, SD ± 3.7, range 19–36) took part in the study which was approved by the Ethical Review Board of the Medical Faculty, University of Tübingen. Each participant was informed about the purpose of the study and signed informed consent prior to participation. Additionally, each participant signed a form informing him or her about potential risks and exclusion criteria of functional magnetic resonance imaging. Participants were payed 8 €/h. All participants had no prior experience with SMR BCI, had no history of neurological diseases and were German native speakers. Psychological measurements before the experiment showed that both groups had equal levels of intelligence using Raven's standard progressive matrices [mean 66.75, (SD ± 19.29), high aptitude users 71.9 (SD ± 8.31), low aptitude users 61.6 (SD ± 25.64), Wilcoxon rank test $p = 0.4$]. The datasets of four participants could not be used in the offline analysis. The dataset of VPTAB was not complete, the anatomical scan of VPTBJ revealed an incidental finding of a brain abnormality (a large portion of the right hemisphere was missing making normalization impossible), a scanner artifact rendered the data from VPTBS useless (frontal signal extinction possibly caused by radio frequency spike artifacts during acquisition due to a mechanical defect) and finally the data of participant VPTBT had missing slices in the structural scan. A detailed overview of EEG-BCI performance, imagery tasks, and demographic data of all participants can be found in Halder et al. (2011). Thus, $N = 9$ subjects were in the low and $N = 7$ subjects in the high aptitude group.

Participants took part in the MRI session depending on individual willingness and suitability. The MRI session was always conducted after the EEG experiement, on average 13.9 days later.

2.2. PROCEDURE

2.2.1. EEG-BCI and neurofeedback

Each of the 20 participants performed a single EEG-BCI session. This included measurements in which the participant had to perform motor execution, observation, and imagery. Three imagery measurements which totalled 75 trials of three classes (left hand, right hand, preferred foot) were used to calibrate the feedback parameters. The calibration trials lasted 8 s, in 4 of which the participant performed the task. After calibration three feedback measurements were performed in which the participant had to use the two classes which showed the highest discriminability in the calibration data to control a cursor. Feedback trials had a length of 9 s, 4 of which with feedback. The additional second was used to indicate which class had to be performed in the current trial. In total 300 feedback trials were performed (150 per class). For a summary of the number of trials per task see **Table 1**. The accuracy the participants achieved in these 300 trials was used to categorize them into high and low aptitude SMR-BCI users by a median split. About 2.5 h were needed for preparation and collecting the calibration data of the system. In total, 5.5–6.5 h were needed to complete the session. For further information and illustrations of the feedback method see Blankertz et al. (2010).

2.3. DATA ACQUISITION

2.3.1. EEG recording

Participants were seated in a chair approximately one meter away from a digital computer screen on which cues and feedback were displayed. The EEG recording was performed using four 32-channel BrainAmp direct current (DC) amplifiers manufactured by Brainproducts, Munich, Germany. A 128-channel cap manufactured by Easy Cap, Munich, Germany was used. Of these 119 were used for EEG recording and positioned according to the extended 10–20 system (Sharbrough et al., 1991), referenced to the nasion and grounded to an electrode between Fz and Fpz. The EEG was recorded at 1000 Hz, band-pass filtered between 0.05 and 200 Hz and notch filtered at 50 Hz. Electromyogram (EEG) artifacts were monitored with bipolar electrodes on both forearms and the participants preferred leg. EOG artifacts were recorded with electrodes placed above and below the right eye for vertical EOG (superior and inferior orbital fossa), and for horizontal EOG with electrodes placed at the outer canthi of the eyes. This data was used to exclude artifact contaminated trials.

Table 1 | Details of EEG experiments.

Motor task	Trial duration	Trials/class	Number of classes
Execution	8 s	25	3
Observation	10 s	20	3
Imagery calibration	8 s	75	3
Imagery feedback	9 s	150	2

Each participant performed motor execution, observation, and imagery used for calibration of the classifier of the BCI and finally motor imagery with SMR-feedback with the optimal combination of two of the three classes (right hand vs. left hand, right hand vs. foot, or left hand vs. foot).

2.3.2. MRI recording

The MRI experiments were performed in a Siemens Magneton Trio Tim 3T whole body scanner using a standard 12-channel head coil. Each subject participated in one DTI measurement ($1.8 \times 1.8 \times 6.5$ mm voxels, 5 mm gap, $TR = 3$ s, $TE = 93$ ms, $FoV = 1150 \times 1150$, Flip Angle $= 90°$, 20 transversal slices, 128×128 voxels per slice, 20 diffusion directions, b-value $=$ 1000 s/mm^2) with the FoV comprising the full cerebrum and parts of the rostral cerebellum (how much of the cerebellum was included was dependent on individual overall brain size). Anatomical images were acquired using a high resolution T1 sequence ($0.5 \times 0.5 \times 1$ mm voxels, 0.5 mm gap, $TR = 1.9$ s, $TE = 2.26$ ms, flip angle $= 9°$, 176 sagittal slices, 448×512 voxels per slice).

2.4. ANALYSIS OF DTI DATA

First, the fractional anisotropy (FA) image from the DTI data was calculated for each individual. Subsequently the normalization parameters to Montreal Neurological Institute (MNI) standard space (using the SPM8 echo-planar imaging (EPI) template) were estimated for the FA-image aligned B0-image of the DTI sequence using SPM Version 8. The normalization parameters were then inverted to warp the standard label image of the ICBM-DTI-81 Atlas into each participants original DTI space, avoiding any interpolation of the original FA values. For each of the 50 ICBM-DTI-81 Atlas regions the median of FA values for all voxels with an FA value above 0.25 was extracted and saved in the participant/regional FA value table.

2.5. ANALYSIS OF ANATOMICAL DATA

We performed a voxel-based morphometry (VBM) Analysis of the T1 weighted anatomical scans to derive descriptors regarding the relative gray matter volume of each Automated Anatomical Labeling (AAL) region as well as the relative white matter volume of each ICBM-DTI-81 Atlas region. The Voxel-based Morphometry Toolbox (VBM5.1) was used for estimation of the individual modulated and unmodulated segmentation outputs. As the modulated outputs can be corrected for non-linear warping only and therefore make any further correction for different brain size redundant, these images can be used directly for volume estimations. For the unified segmentation approach—repeated segmentation, bias correction, and warping iterations as described in Ashburner and Friston (2005)—used in this study the tissue probability maps provided within the SPM5 template set were used because the subjects were drawn from the appropriate population. We applied the thorough clean-up option of the VBM toolbox and a medium Hidden Markov Random Field model for denoising of the T1 image. A check of sample homogeneity of the modulated images [using the standard deviation (SD) approach within VBM5.1] revealed that the VBM results of the images were all within a tolerable range (not considering the previously excluded participants). In order to smooth the resulting images we applied a three dimensional Gaussian smoothing kernel (FWHM $= 3$ mm, significantly below the rounded cubic root of the volume of the smallest AAL-region in equal voxel-space). Subsequently the images were re-sliced into the $1 \times 1 \times 1$ mm voxel space of the atlas images containing the respective region labels. For each AAL and ICBM-DTI-81 Atlas region the number of gray matter and white matter voxels within the atlas derived volumes of interest was counted—equalling the regional volume of the respective tissue relative to the entire individual brain. These volume values are strongly correlated across our healthy sample as they all measure brain volumes for identical regions. The total raw volume values [ml] for each participant were also extracted, resulting in absolute volume estimates of the individual amount of gray matter, white matter, and cerebro-spinal fluid (CSF) and the respective gray/white matter ratio.

2.6. CATEGORIZATION INTO HIGH AND LOW APTITUDE USERS

The anatomical data extracted with the methods described in the previous sections was used to predict the performance of the participants. Prediction was performed with four distinct feature sets calculated as described in the previous section: relative gray matter volume, relative white matter volume, FA values and total raw volumes of gray and white matter, CSF and gray/white matter ratio. Shrinkage linear discriminant analysis (LDA) was used to classify the participants into high and low aptitude users Blankertz et al. (2011). Participants were assigned to one of the two groups based on their performance in the EEG-BCI experiment. The classifier performance was validated using a leave-one-participant-out cross validation scheme. At the beginning of each cross validation step features were selected from the current training set based on the significance of the correlation (Pearson's r, $p < 0.1$) between feature and BCI performance (all excluding the test set). Then the classifier was trained using these features and was applied to the test set (the participant that was not included in the current training). All features were scaled to [0, 1].

3. RESULTS

3.1. EEG-BCI ONLINE ACCURACY

The median EEG-BCI performance of the 20 participants was at 82.1%. This value was used to split the participants into high and low aptitude BCI users. After the exclusion of the four participants mentioned in the Methods section this resulted in 7 high and 9 low aptitude users. Further details on the sample can be found in Blankertz et al. (2010); Halder et al. (2011), and Hammer et al. (2012).

3.2. PERFORMANCE PREDICTION RESULTS

All reported results are based on the leave-one-participant-out cross validation scheme described in the Methods section. If none of the features fulfilled the inclusion criteria in the current step an accuracy of 0.5 (chancel level) is assumed. Using relative gray matter, relative white matter or absolute gray/white matter led only to chance level performance prediction. Using the FA features led to an error of 6.25% (binomial test to quantify significance of prediction $p < 0.0001$). This means that only one

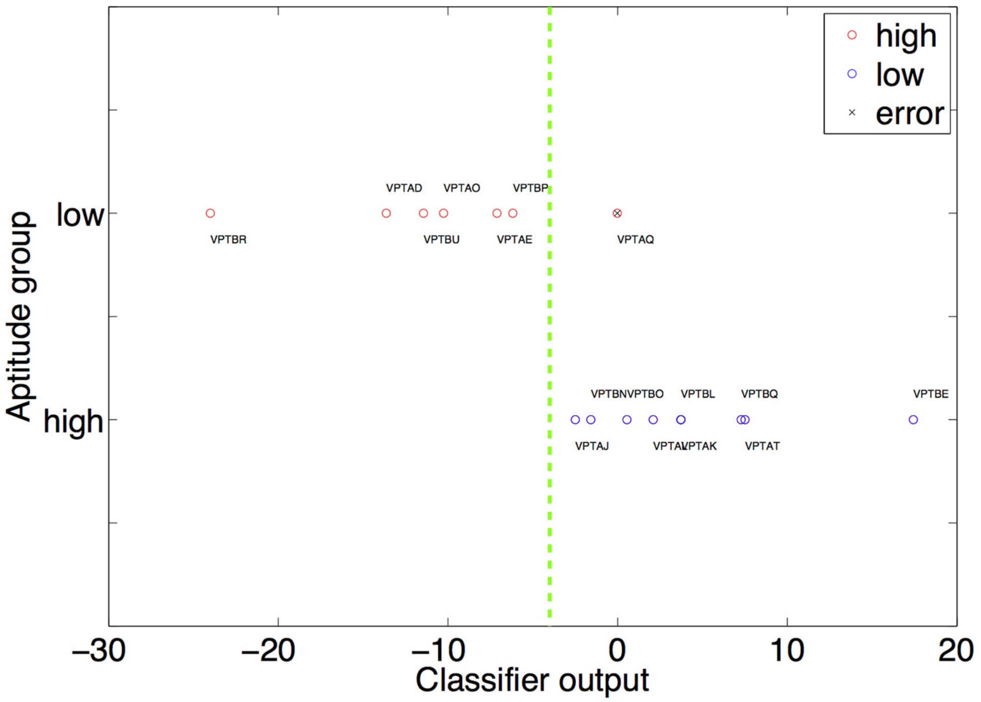

FIGURE 1 | The result of the multiplication of the weight and feature vector is shown on the x-axis. The high and low aptitude users are grouped on two separate horizontal lines on the y-axis (red circles high aptitude users, blue circles low aptitude users). This is only used to visually differentiate high from low aptitude users visually. The decision plane used by the classifier therefore has to be a horizontal line (dashed green line). It is optimally placed anywhere between VPTBP and VPTAJ. This placement causes the single error in our classification procedure (prediction of the group of VPTAQ, marked by a black "x"). The weights used to calculate the position of each participant are the ones obtained when this participant comprises the test dataset.

Table 2 | Correlations between FA value and BCI performance of the regions used most often for prediction of the aptitude group.

Correlation	*p*-value	Significant	ICBM-DTI region code	Abbreviation	Region	Feature usage (%)
0.63	0.009	Yes	38	CGH-R	Cingulum (Hippocampus) right	100
0.54	0.029	Yes	43	SFO-L	Superior Fronto-Occipital Fasciculus left	100
0.54	0.032	Yes	4	BCC	Body of Corpus Callosum	100
0.52	0.040	Yes	15	CP-L	Cerebral Peduncle left	100
0.51	0.043	Yes	28	PCR-R	Posterior Corona Radiata right	87.5
0.50	0.051	No	34	EC-R	External Capsule right	100
0.48	0.060	No	1	MCP	Middle Cerebellar peduncle	87.5
0.47	0.065	No	16	CP-R	Cerebral Peduncle right	93.75
0.21	0.429	No	17	ALIC-L	Anterior limb of Internal Capsule left	81.25
−0.01	0.956	No	21	RLIC-L	Retrolenticular part of Internal Capsule left	68.75

Only correlations above the second to last horizontal black line are significant (FDR corrected, $p < 0.05$).

participant (VPTAQ, see **Figure 1** for a graphical representation of the classifier output) was classified incorrectly. The number of times each feature was selected for classification is given in **Table 2**.

3.3. SELECTED FEATURES

The T1-based anatomical MRI information (rel. GM, rel. WM, and absolute GM/WM/CSF/TIV) could not be used to predict the performance category of the participants of this study. Therefore, all selected features originated from the regionwise extraction of average local FA values for the regions described in the ICBM-DTI-81 Atlas. See **Table 2** for the number of times each feature was selected. The areas with highest discrimination were the Body of Corpus Callosum (regioncode 4, selected in 16 CV-folds), the right Cerebral Peduncle (regioncode 15, selected in 16 CV-folds), the right External Capsule (regioncode 34, selected in 16 CV-folds), the right Cingulum at Hippocampus (regioncode 38, selected in 16 CV-folds), the left Superior Fronto-Occipital Fasciculus (regioncode 43, selected in 16 CV-folds), the left Posterior limb of the Internal Capsule (regioncode 16, selected in 15 CV-folds), the Middle Cerebellar Peduncle (regioncode 1, selected in 14 CV-folds), the right Posterior Corona Radiata (regioncode 28, selected in 14 CV-folds), the right Posterior limb of the Internal Capsule (regioncode 17, selected in 13 CV-folds) and the right rentrolenticular part of the Internal Capsule (regioncode 21, selected in 11 CV-folds). Seven further white matter regions (regioncodes 5, 10, 14, 26, 41, 46, and 49) were selected in only one CV-fold. White matter regions with high discriminatory value are illustrated in **Figure 2**.

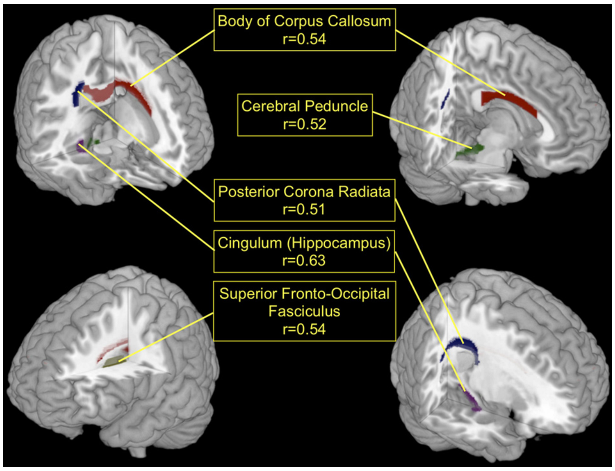

FIGURE 2 | The top five white matter regions which were most discriminating in the low vs. high BCI-aptitude group comparison (based on feature use over CV-folds) and showed significant correlations (FDR corrected, $p < 0.05$) with individual BCI-performance. Red, Body of Corpus Callosum; Green, left Cerebral Peduncle; Blue, right Posterior Corona Radiata; Lilac, right Cingulum (Hippocampus area); Yellow, left Superior Fronto-Occipital Fasciculus.

3.4. CORRELATION OF LOCAL FRACTIONAL ANISOTROPY AND EEG-BCI PERFORMANCE

After identifying local FA as the most discriminating feature, the top-discriminating WM regions were selected (based on selection in CV-folds) and local FA values were correlated with individual accuracy (as described in section EEG-BCI and Neurofeedback), as a measure of EEG-BCI performance. The correlations in the Cingulum at Hippocampus, left Superior Fronto-Occipital Fasciculus, Body of Corpus Callosum, left Cerebral Peduncle, and the right Posterior Corona Radiata showed positive correlations (0.51–0.63) with the individual accuracy (FDR corrected, $p < 0.05$). Note that these significances are calculated over the whole dataset whereas the significances used for feature selection were calculated over the subsets of the corresponding cross-validation fold. This can lead to discrepancies such as the FA value of the retrolenticular part of internal capsule left being included in the majority of the folds but still having a large *p*-value if correlated with individual accuracy over full data set. Higher FA in these regions of the brain is related to better individual EEG-BCI performance. This is shown in **Figure 2** for the regions whose FA values correlate the strongest with BCI performance. An overview of all regions used during the prediction of the aptitude group is given in **Table 2**. For comparison purposes we applied the predictor presented in Blankertz et al. (2010) to the data of this study. The resting SMR-based predictor correlates with accuracy with $r = 0.73$ ($p < 0.01$) in this sample.

4. DISCUSSION

Using only structural MRI data we were able to predict with 93.75% accuracy which aptitude group a participant belonged to according to his or her EEG-BCI performance. This prediction was possible using structural features extracted from DTI images (specifically the FA value), but not using structural features extracted from T1 images. Strong significant correlations between BCI performance and FA values of the region of interest (ROI) defined in the AAL atlas were found for right Cingulum, left superior Fronto-occipital Fasciculus, Body of Corpus Callosum, left Cerebral Peduncle, and right posterior Corona Radiata (see **Table 2** for details). Even though the correlation of the FA-values (e.g., the cingulum in **Table 2**) in this study with BCI accuracy is weaker than the correlation of the SMR amplitude with accuracy ($r = 0.63$ vs. $r = 0.73$) we believe that the presented data is a valuable contribution to the construction of a comprehensive model of BCI performance in addition to the data that is already available (Blankertz et al., 2010; Kleih et al., 2010; Grosse-Wentrup et al., 2011; Halder et al., 2011, 2013; Kaufmann et al., 2011; Hammer et al., 2012). This knowledge can be used to design novel BCI training paradigms which specifically increase the microstructural integrity of central white matter.

Local FA values can be an indicator of myelinization quality, which is critical to the maintenance of appropriate conduction velocities for interregional communication in the brain. It is noteworthy that Valdés-Hernández et al. (2010) report a statistical relation of the spectral position of the alpha peak or the alpha frequency and FA values in a large sample of 222 participants in regions similar to those identified here. Thalamocortical/corticothalamic fibers, commissural fibers, and association fibers such as parts of the Fronto-Occipital Fascicles show a relation to EEG measures also in their sample. In accordance with our findings on TIV and relative volume estimations, purely volumetric anatomical MRI information (head size and neocortical surface area) did not yield any significant relation with the EEG measures in Valdés-Hernández et al. (2010). The probability of an association between EEG phenomena and the structure of thalamocortical connections rather than the thalamus itself, which would have shown in our anatomical volumetric analysis (e.g., through structures such as the thalamocortical parts of the corona radiata) is strengthened by our present data.

Further, both Whitford et al. (2010) and Teipel et al. (2009) report an association of white matter FA in commissural regions with interhemispheric transfer times (Whitford et al., 2010), as well as an association of FA in the middle Cerebellar Peduncle, the Cingulum and frontal and occipital white matter with measures of interhemispheric alpha coherence at various sites (Teipel et al., 2009).

While activity in the alpha-band and the SMR are phenomena which emerge from distinct neurophysiological origins their frequency (Alpha 8–12 Hz, SMR 8–15 Hz) overlaps considerably and both are generated through thalamo-cortical loops. With regard to the strong association of white matter FA and phenomena within these frequencies it is possible, that localized differences in white matter structural integrity are most apparent in these EEG features.

With respect to the SMR, the fact that discriminatory information could be found in the present sample in white matter structures associated with the somatomotoric system (Internal Capsule, Cerebral Peduncle, Middle Cerebellar Peduncle) indicates that microstructural characteristics of the white matter system connecting motor and somatosensory regions within the brain and with the periphery are highly relevant to the formation of an individual SMR and the ability to utilize it for communication and control.

The fact that extra-motoric white matter tracts (e.g., the Fronto-Occipital Fasciculus) also contained information for the discrimination suggests, that these tracts—connecting higher order association cortices—are critical for the large-scale integration and intentional modulation of the SMR via motor imagery. Successful motor imagery requires the recollection of memorized kinesthetic percepts, the assembly of these percepts into a coherent mental image and the ability to intentionally manipulate that mental image by performing sequences of imaginary movements. The microstructure of cingular white matter in the vicinity of the Hippocampus might be responsible for the recollection process, while interhemispheric and fronto-occipital tracts affect imagery and control of that mental image in the frame of the entire BCI task.

Whether such differences—found in the domain of structural traits and functional activation differences (Halder et al., 2011)—all originate from a latent factor which causes these differences and also influences BCI-aptitude, or whether the identified features are of causal relevance for BCI-aptitude themselves can only be resolved by future experiments.

Although based on the present data a link between local FA and BCI performance seems highly intuitive, the underlying causal mechanism remains only poorly understood. In order to investigate a causal link between psychological (Hammer et al., 2012) and neurophysiological predictors of BCI performance with white matter properties we need to record DTI in a larger sample of BCI-users that is as well assessed psychologically. A hypothetical relationship of conduction velocity and local FA could be investigated by combining an interhemispheric transfer time experiment (Whitford et al., 2010) with an assessment of BCI performance. Furthermore, a relationship between EEG features in the Alpha/SMR frequency domain could be characterized further by systematically associating these phenomena with FA measures from a large population, in which the metrics in question vary across a considerable range. More sophisticated DTI measurement schemes with a higher number of applied diffusion directions and better spatial resolution will enable the reconstruction of white matter tracts using tractography methods, which could provide an indication whether the observed differences in local FA merely originate from variations across the dimension of myelinization quality/tissue integrity or whether the anisotropy of some diffusion tensors is reduced due to a higher number of crossing, kissing, or splitting fiber tracts in the voxels of the deep white matter structures in question. Such a finding could indicate more diverse white matter wiring patterns in subjects with low local FA in these structures, rather than indicate variations in myelinization quality. Graph theoretical analysis of white matter connectivity in BCI-users could bring new insights regarding this question and is already beginning to be explored (Buch et al., 2012).

A real time-fMRI training (Caria et al., 2010; Lee et al., 2011) for voluntary up-regulation of SMA-activity (Halder et al., 2011) or extensive training-interventions to increase the FA in the identified white matter regions could yield further insight into the role of these features in the formation of individual BCI-aptitude. Recently it has been shown that extensive training with an EEG-BCI increases motor cortex responsiveness (assessed with transcranial magnetic stimulation) and also the global efficiency index of the scalp electrode connectivity matrix (Pichiorri et al., 2011). It is conceivable that these changes will also be reflected in a change of FA values. Such an association between white matter connectivity features (such as FA) and the factors that influence motor learning (such as SMR features) is subject of ongoing research in the area of stroke rehabilitation (Buch et al., 2012).

One of the central purposes of BCI is their potential to enable communication in patients with progressive degeneration of the motor system such as ALS. While ALS was long considered a disease with mainly motor system specific cerebral involvement, this notion is changing in the light of recent findings on the extensive involvement of extra-motor white matter structures such as the Corpus Callosum (Filippini et al., 2010), Cingulum (Woolley et al., 2011), Uncinate Fasciculus (Sato et al., 2010) or in regions such as the Insula, Hippocampus, the ventrolateral Pre-motor Cortex (PMC), Parietal Cortex, and bilateral Frontal Cortex (Senda et al., 2011). Based on these findings it can be assumed that the pathology in late-stage ALS spreads to multiple central white matter regions, which may be considered critical for the control of those EEG features that are presently used in most BCI applications (e.g., P300, SMR), hence impairing the ability of the patients to utilize present BCI. Birbaumer et al. (2008) proposed that in complete locked-in state (CLIS) output oriented goal directed thinking and imagery impedes and extinguishes instrumental learning of BCI-control leading to an inability of these patients to communicate (Kübler and Birbaumer, 2008). The dysfunctional fiber structure may thus be the consequence or the cause of this deficit.

Fortunately, the notion that white matter microstructure and connectivity no longer change in the adult brain had to be corrected in the light of present findings on the effectiveness of learning interventions such as meditation (Tang et al., 2010), training of working memory (Takeuchi et al., 2010), or juggling training (Scholz et al., 2009) in increasing local FA in certain motor and extra-motor structures—indicating that counter-measures against the deterioration of central white matter in certain pathologies and for the maintenance of individual BCI-aptitude for late-stage communication in ALS should be possible.

Besides for communication, BCIs are being used more and more for other applications such as motor restoration in patients with stroke or other brain damage (Birbaumer et al., 2008; Silvoni et al., 2011). In this field in particular a reliable prediction of BCI aptitude is useful due to the high amount of effort and time involved in this form rehabilitation. In addition to this MRI scans are routinely performed as part of the diagnosis and the DTI data can thus be collected with only a small amount of additional effort. In addition BCI technology has also been used to detect if patients with disorders of consciousness can follow commands, often using MRI, but recently also using EEG (Owen et al., 2006; Lulé et al., 2013). In both usage scenarios, success is already important on a single case basis. Thus, we believe the additional effort of collecting DTI data, that will make successful communication more probable, to be easily justifiable.

The data presented in this paper does not explain 100% of the variance of performance. Thus, other factors besides the ones evaluated here must influence BCI performance. Besides the dependency of performance on brain structure psychological factors such as motivation have been shown to have an influence (Kleih et al., 2010; Hammer et al., 2012). In addition to this physiological traits such as heart-rate-variability or the amplitude of the resting state SMR have been shown to impact BCI performance (Blankertz et al., 2010; Kaufmann et al., 2011). Another aspect of performance will be influenced by more transient factors such as the current level of fatigue or attentiveness. Thus, one limitation of the current study is that the session-to-session stability of the investigated factor was not investigated. Finally, to gain a conclusive predictor of performance all of the aforementioned factors will have to be integrated into a single model.

5. CONCLUSIONS

Microstructural characteristics of cerebral white matter have a strong (93.75% correct prediction) predictive power of SMR-BCI performance, which may have implications for these training procedures. We can assume that the identified white matter traits will not change within a single session of BCI training. Therefore, our findings indicate that the best strategy of improving BCI performance in low aptitude users is by conducting a long-term BCI training program consisting of multiple sessions, that does not only target to increase proficiency in BCI usage for communication and control but attempts to incorporate interventions that increase or stabilize the microstructural integrity of BCI-critical central white matter.

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The morphology of midcingulate cortex predicts frontal-midline theta neurofeedback success

Stefanie Enriquez-Geppert[1,2], René J. Huster[1,3], Robert Scharfenort[1], Zacharais N. Mokom[1], Johannes Vosskuhl[1], Christian Figge[2], Jörg Zimmermann[2] and Christoph S. Herrmann[1,3]*

[1] Department of Psychology, European Medical School, Carl von Ossietzky University, Oldenburg, Germany
[2] Karl-Jaspers Clinic, European Medical School, Carl von Ossietzky University, Oldenburg, Germany
[3] Research Center Neurosensory Science, Carl von Ossietzky University, Oldenburg, Germany

Edited by:
Guilherme Wood,
Karl-Franzens-University of Graz,
Austria

Reviewed by:
Lutz Jäncke, University of Zurich,
Switzerland
John H. Gruzelier, University of
London, UK

***Correspondence:**
Christoph S. Herrmann, Department
of Psychology, European Medical
School, Carl von Ossietzky
University, Ammerländer Heerstr.
114-118, 26111 Oldenburg, Germany
e-mail: christoph.herrmann@
uni-oldenburg.de

Humans differ in their ability to learn how to control their own brain activity by neurofeedback. However, neural mechanisms underlying these inter-individual differences, which may determine training success and associated cognitive enhancement, are not well-understood. Here, it is asked whether neurofeedback success of frontal-midline (fm) theta, an oscillation related to higher cognitive functions, could be predicted by the morphology of brain structures known to be critically involved in fm-theta generation. Nineteen young, right-handed participants underwent magnetic resonance imaging of T1-weighted brain images, and took part in an individualized, eight-session neurofeedback training in order to learn how to enhance activity in their fm-theta frequency band. Initial training success, measured at the second training session, was correlated with the final outcome measure. We found that the inferior, superior, and middle frontal cortices were not associated with training success. However, volume of the midcingulate cortex as well as volume and concentration of the underlying white matter structures act as predictor variables for the general responsiveness to training. These findings suggest a neuroanatomical foundation for the ability to learn to control one's own brain activity.

Keywords: neurofeedback success, brain structure, fm-theta enhancement, midcingulate cortex, cingulate bundle

INTRODUCTION

One of the most promising neuroscientific approaches for the enhancement of cognition and task performance, and eventually even for the treatment of psychiatric mental disorders, is neurofeedback (e.g., Enriquez-Geppert et al., 2013a). Neurofeedback is a form of brain computer interfaces (BCI); whereby neural parameters are fed-back to a human subject for up- or down regulation of one's own brain activity (e.g., Hinterberger et al., 2003; Bauerfeind et al., 2011; Scherer et al., 2013). Neurofeedback has been shown to be effective in the therapy of, among other conditions, attention deficit hyperactivity disorder (ADHD; e.g., Birbaumer et al., 2009) leading to a significant reduction in symptom severity even lasting for more than 2 years (Gani et al., 2008). Improved cognition and neurophysiological functioning due to neurofeedback training has also been demonstrated in healthy subjects (e.g., Egner and Gruzelier, 2001). Neurofeedback is based on trial-to-trial modulations of the ongoing neural activity, for instance on the modification of cortical oscillations (e.g., Enriquez-Geppert et al., 2013b). Participants play an active role while utilizing the real-time feedback based on the online-analysis of the brain activity in order to learn how to influence their own brain functions. This feedback loop hence adheres to operant conditioning principles. Finally, neurofeedback constitutes an inexpensive and non-invasive intervention tool.

Recent years have seen significant advances in technology and the investigation of cortical oscillations which have also impacted the advancement of neurofeedback approaches. For example, oscillations have gained much interest as a manifestation of neural mechanisms enabling brain communication and cognition (e.g., Herrmann et al., 2004). It has been shown that oscillations index sensory and cognitive processes, as for example seen with stimulus-induced amplitude changes (e.g., Basar et al., 2001). Other examples are augmentations of power in theta and alpha frequency bands with increasing task demands (e.g., Klimesch, 1999; Mitchell et al., 2008; Cohen and Cavanagh, 2011). Thus, the identification and usage of a particular oscillation, corresponding to a specific cognitive process that is to be modified, is of crucial importance for any neuroscientific intervention. For example, Keizer et al. (2010) revealed different behavioral effects of two neurofeedback protocols to increase either local gamma band or local beta band activity associated with a long-term memory task. The former modulation led to improved recollection, the latter to improved familiarity. Further emphasizing causal relationships between brain oscillations and cognition, it was shown that the manipulation of slow potential oscillations enhances memory retrieval after learning (Marshall et al., 2006), or that detection thresholds of auditory stimuli depend on the phase of an entrained 10 Hz oscillation during which stimuli are presented (Neuling et al., 2012).

While traditionally the number of neurofeedback training sessions is relatively high in clinical studies (up to 30 or 40 sessions), the utilization of individualized neurofeedback in healthy participants has been shown to succeed with substantially less sessions. Individualized neurofeedback refers to the individual determination of a specific frequency band for each participant. Frequency bands have been shown to vary considerably between subjects as a function of age, neurological diseases, and brain volume (Klimesch, 1999). Thus, individually determined frequency peaks might differ substantially between subjects, and may well be located at or beyond the border of another frequency band. Hence, using roughly fixed frequency bands irrespective of a single subject's brain state might not be optimal for neurofeedback training success. With this in mind, Zoefel et al. (2010) demonstrated the relevance of individualized alpha band neurofeedback training for the performance in mental rotation tasks with only five training sessions.

Despite the general success of neurofeedback trainings, studies often report a substantial amount of so-called non-responders: participants who do not show any modulation of their brain activity in response to a neurofeedback protocol (e.g., Hanslmayr et al., 2005; Doehnert et al., 2008; Zoefel et al., 2010; Enriquez-Geppert et al., 2013b). In 1995, Lubar and colleagues (Lubar et al., 1995) reported that 37% of their sample did not show modulated EEG activity after 40 sessions of neurofeedback training. Furthermore, in a continuous performance task on attention, retested after the training, these non-responders showed less improvement of performance than responders. Among others, Fuchs et al. (2003) have reported a similar subgroup that was not able to control their EEG activity after a comparably long training duration of 36 sessions.

Other studies have even reported a complete lack of behavioral effects with non-responders. For instance, in a study by Hanslmayr et al. (2005), neurofeedback success was strongly correlated with the enhancement of cognitive performance in a mental rotation task in healthy subjects. However, non-responders did not show any performance improvements. Similarly, Drechsler et al. (2007) reported neurofeedback training of slow cortical potentials in children with ADHD. Again, a subgroup of participants neither learnt to control their EEG during the course of neurofeedback nor did they show a decrease of clinical symptoms. Only the responders' training success was correlated with the regulation of disrupted behavior concerning the clinical symptoms of inhibition and impulsivity.

However, far too little attention has been paid to assess or even to predict and to explain non-responsiveness to neurofeedback (exceptions are Kotchoubey et al., 1999; Neumann and Birbaumer, 2003). One of the few studies investigating neurofeedback success focusing on sensori-motor rhythms (SMR; 12–15 Hz) was published by Weber et al. (2011). Here, early training success was positively correlated with the ability to regulate one's own brain activity at the end of training. Weber et al. (2011) further presented a classification scheme to determine responders vs. non-responders early in training. While this work is highly relevant for practical reasons, namely the possibility to early assign participants to appropriate interventions, still the mechanisms underlying these differences were not clarified. Addressing differences in individual strategies for EEG modulations, Nan et al. (2012) analyzed the association of mental strategies with training success in an upper alpha band neurofeedback training study, and reported strategies related to positive thinking to be the most successful ones. As suggested by Gruzelier et al. (1999), based on results of their study with schizophrenic patients who were less efficient in controlling their slow potential inter-hemispheric asymmetry, a lapse of concentration may as well play a role for decreased training success. In healthy participants, however, motivation and commitment to training may be more important for training success. To investigate this issue, Enriquez-Geppert et al. (2013b) assessed motivation and commitment by subjects' self-reports. However, a lack of motivation or commitment was not observed with non-responders.

A neglected issue with regard to the understanding of neurofeedback success concerns possible structure-function associations. That is, structural determinants of oscillations that are critical to neurofeedback success have rarely been focused on up to now. Recently, Halder et al. (2013) reported that deep white matter structures were correlated with BCI-performance.

With regard to the domain of behavioral training, more studies on brain function and learning success have been conducted. For instance, correlations between learning outcome and brain structure have been shown for language learning (e.g., Loui et al., 2011; Wong et al., 2011) and video game skill acquisition (e.g., Raz et al., 2000; Basak et al., 2011). In a grammar learning study, integrity of white matter tracts near the left Broca's area was correlated with training success (Flöel et al., 2009). In a video game skill training study, the volume of the dorsal striatum was correlated with enhanced gaming performance at the end of training (Erickson et al., 2010).

An oscillatory candidate for neurofeedback targeting the enhancement of high-order cognitive processes, such as executive functions, is frontal-midline (fm)-theta. Executive functions are known to enable the planning, controlling and monitoring of complex, goal-directed behavior and thoughts (Seiferth et al., 2007) and are associated with various behavioral and neurocognitive impairments when disrupted (e.g., Goldberg and Seidmann, 1991). When cognitive processing is enhanced, fm-theta shows an increased amplitude (Mitchell et al., 2008). Fm-theta enhancement has furthermore been related to event-related brain potentials; the so-called fm-negativities that are commonly observed in different tasks involving interference in information processing [e.g., the N200, the event-related negativity (ERN); Falkenstein et al., 2000; Nigbur et al., 2011]. Thus, fm-theta has been proposed as a universal mechanism for action monitoring with the midcingulate cortex (MCC; often referred to as dorsal anterior cingulate cortex) acting as hub for the integration of information (Cavanagh et al., 2012). However, a significant degree of inter-individual variability has been found concerning the peak frequency of fm-theta, while intra-individually the fm-theta frequency was found to be constant across time (Näpflin et al., 2008).

Regarding fm-theta neurofeedback, inter-individual differences concerning the ability to enhance their individual fm-theta amplitude have been shown, and non-responders have been identified as well (Enriquez-Geppert et al., 2013b). A main question therefore is, whether differences in the morphology of putative fm-theta generators are related to the ability to up-regulate brain activity utilizing neurofeedback. Related work showed that increased amplitudes of the N200 in the context of conflict monitoring tasks were found to be related to grossy-morphometric characteristics of the cingulate cortex, such as the occurrence of a second cingulate gyrus (Huster et al., 2007, 2009a,b, 2012). However, it has also been suggested that the MCC serves as a hub for information flow, using fm-theta to functionally interact with other cortical and subcortical areas (e.g., Cohen, 2011; Cavanagh et al., 2012). Thus, on the one hand, learning to increase fm-theta amplitudes might depend on the ability to recruit or synchronize the activity of midcingulate neurons, whose numbers are associated with regional volume and gross-morphology; on the other hand, white matter characteristics, such as increased bundle volumes, axonal density, or myelination, may ease the interregional synchronization of fm-theta oscillations (Cohen, 2011).

The aim of this paper is to determine potential relationships between fm-theta neurofeedback success and brain structures known to be critically involved in the generation of fm-theta. We built upon an individualized, eight-session fm-theta neurofeedback training. First, it is assessed whether early responsiveness to fm-theta neurofeedback is related to final training outcome as was already shown for SMR (Weber et al., 2011) and slow cortical potentials (Neumann and Birbaumer, 2003). Then, the association of structural characteristics of the MCC and fronto-cortical areas with fm-theta training success is examined. More specifically, it was investigated whether gray and white matter volume or concentration is associated with training success.

MATERIALS AND METHODS

PARTICIPANTS

Nineteen healthy participants took part in the experiment (11 women; mean age: 24 years, standard deviation: 2.7 years). We used the data of 14 subjects of our previous study (Enriquez-Geppert et al., 2013b) and acquired new data from another five subjects in order to have sufficient number of subjects for the current analysis. They were all right-handed as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971), with a normal or corrected to normal vision. All gave written consent to the protocol approved by the ethic committee of the University of Oldenburg, and received a monetary reward of 8 € per h. The study was conducted in accordance with the Declaration of Helsinki.

STUDY PROCEDURE

First, participants were invited for two separate sessions that were scheduled in rapid succession. During the first session, structural MR-images were taken at a local hospital (Pius Hospital, Oldenburg, Germany) according to the protocol specified below. On a second appointment, which took place at the Department of Psychology of the University of Oldenburg (Germany), a cognitive test-battery of executive function tasks (comprising the stop-signal, Stroop, n-back, task-switching task) with concurrent EEG recordings was performed in order to identify the individual's dominant fm-theta frequency. The individual fm-theta frequency was subsequently used for an individualized neurofeedback. These measurements were always done on the first working day of a week. The actual neurofeedback training started the following day (Tuesdays). The individualized fm-theta neurofeedback training consisted of eight sessions in total, spread over the course of 2 weeks, ending the Thursday of the second week.

MRI SCANNING PROTOCOL

The acquisition of the individual anatomical scans was obtained on a 3 Tesla MRI scanner (Siemens Magnetom Verio) equipped with the standard bird cage head coil at the Pius Hospital of Oldenburg, Germany. Participants' heads were stabilized by using foam cushions to minimize movement-related artifacts. Generalized Autocalibrating Partially Parallel Acquisition was used to obtain 176 contiguous T1-weighted ($TR = 1900$ ms, $TE = 2.52$ ms) 1 mm thick slices in the sagittal plane with a 256×256 matrix size and a field of view of 250×250 mm^2, resulting in an in-plane resolution of 0.98×0.98 mm^2.

PROCESSING OF MR-IMAGES

First, the subjects' images were individually co-registered and normalized to MNI reference space. Images were then segmented using the iterative unified segmentation approach. In addition to concentration values, modulated images were computed to allow for voxel-wise volumetric comparisons. In short, modulated images are computed by scaling the concentration images based on parameters of previous normalization steps such that the total amount of regional gray matter is preserved. Concentration and modulated volume images were computed for both gray and white matter. Data were smoothed with a Gaussian kernel of 8 mm FWHM. Details on the exact procedures can be found in Ashburner and Friston (2009) and the SPM8 manual available at www.fil.ion.ucl.ac.uk/spm.

REGION OF INTEREST ANALYSES

After processing of the images for each subject, mean values for a selected number of cortical areas were computed by masking images with regions of interest (ROI) derived from gray matter and white matter atlases specified below. Gray matter regions were selected according to their relevance for being potential generators of fm-theta. According to Mitchell et al. (2008), at least two sources of fm-theta are to be differentiated. The MCC has been implicated to be the main generator of fm-theta, especially in context of demanding cognitive tasks relying on cognitive control. On the other hand, regions of superior, middle, and inferior frontal cortices have been suggested to either generate or to rely on fm-theta as transfer signal. Hence, for each hemisphere the MCC, superior and middle frontal cortices, as well as pars triangularis, orbitalis, and opercularis of the inferior frontal cortex (IFC) were extracted using the templates provided by the software package Automated Anatomical Labeling (AAL; Tzourio-Mazoyer et al., 2002). Whereas one might argue that the power of fm-theta activity relies on gray matter characteristics such as the number of synchronized neurons, the individually dominant frequency, for example, rather might rely on features of underlying white matter tracts, reflected in the cingulate bundle (e.g., Valdés-Hernández et al., 2010; Nunez, 2011; Zaehle and Herrmann, 2011). The cingulate bundle is located below the MCC in its rostro-caudal course and is supposed to consist of associative fibers originating and terminating in cingulate regions, but also connecting to the prefrontal cortex (Schmahmann et al., 2007). Similarly, bilateral superior longitudinal fascicle II (SLF) were extracted, which represent an interhemispheric bi-directional tract connecting the prefrontal with the parietal cortex (e.g., Makris et al., 2005). Lastly, bilateral white matter structures of the anterior and superior corona radiate were extracted that connect the prefrontal cortex with the thalamus and deep brain structures (Mori et al., 2005; Schmahmann and Pandya, 2006). White matter ROIs were extracted from the JHU white-matter tractography atlas (Hua et al., 2008).

EEG RECORDINGS, COGNITIVE TEST BATTERY, AND NEUROFEEDBACK TRAINING

All EEG recordings were performed in an electrically shielded and sound attenuated room using the Brain Vision Recorder software in combination with BrainAmp EEG amplifiers (Brain Products GmbH, Gilching, Germany). Electrode impedances were kept below 5 kΩ with nose as an online reference.

Before neurofeedback started, the individual fm-theta frequency of each subject was determined based on the estimation of the cognitive test battery of executive function tasks. (1) A visual number-letter task was applied for task-switching. Numbers had to be classified into even or odd, letter into vowels or consonants via a right or left hand button press. Depending on the background color, participants had to switch between number and letter processing (switch condition) or to continue (no switch condition). (2) An alternating three-back-, zero back task was used for memory updating, containing letters as stimuli. During the three-back task, participants were instructed to identify those letters, which were presented exactly three trials before (updating condition). During zero-back task, participants had to indicate those letters presented at the beginning (no updating condition). (3) A visual stop-signal task was applied for response inhibition. In the majority of trials, participants reacted with left and right button presses (go condition) according to left and right arrows, however, whenever as stop-signal followed, announced by a color change of the arrows, subjects had to abort their initiated response (stop condition). (4) For conflict monitoring the Stroop task was utilized. Color names were presented and participants had to respond according to the ink color of the color names via left hand or right hand button press. The ink colors either corresponded to the presented color names (congruent condition) or not (incongruent condition). During task processing, EEG was recorded from 32 electrodes while subjects performed the cognitive test battery. Preprocessing of the concurrently recorded EEG data was accomplished by means of EEGLAB (freely available from http://www.sccn.ucsd.edu/eeglab). EEG recordings were filtered with low-pass (80 Hz) and high-pass filters (0.5 Hz), and down-sampled to 250 Hz. Eye artifacts were corrected by an infomax independent component analysis (ICA; Bell and Sejnowski, 1995; Makeig et al., 2004), and incorrect responses were discarded. For each the inhibition condition of the stop-signal task, the conflict condition of the Stroop task, the updating condition of the three-back task, and the switching condition of the task-switching task, individual fm-theta frequency peaks were identified in the range of 4–8 Hz of the event-related spectral perturbation (ERSP). These task-specific fm-theta frequencies were averaged and used for the individualized neurofeedback training.

For the neurofeedback, EEG activity was recorded at seven electrodes (Fz, FC1, FCz, FC2, Cz, Fp1, and Fp2) with an online nose reference and read out in real-time. Data was processed by in-house software programmed in Matlab 7.14 (the MathWorks, Natrick, USA) by performing Fast Fourier-Transforms (FFT) with a hamming window every 200 ms on a sliding 2 s data window. During training sessions, ocular artifacts were detected at Fp1 and Fp2. Before each training session, an EOG calibration was conducted to support the detection and the rejection of eye blinks. During this EOG calibration, time frames containing eye artifacts were identified based on an individually adapted amplitude threshold. Artifact-specific peak amplitudes were then identified and extracted from an FFT. Based on this individual frequency peak, an individualized eye artifact-related frequency band was calculated and used during the following measurements in order to reject every trial (2 s data window) containing artifacts. Feedback was given in form of a colored square presented on a computer desktop. To increase individual fm-theta activity, participants were instructed to color the square red as long and saturated as possible by applying mental strategies (e.g., mental operations, emotions, imaginations etc.).

At the beginning of each session, the above mentioned EOG calibration was performed. The neurofeedback training sessions themselves consisted of 6 training blocks (block 1–6) each lasting five min with short breaks in between. Before and after these training blocks, further 5 min blocks were recorded; these were the so-called start and end baseline measurements during which no feedback was given. During these measurements the color of the square slowly altered between red, gray, and blue. Participants were instructed to count the red gradients, but not to use any mental strategy and to rest with eyes open. The start baseline measurement of each particular training session was used as reference for the feedback in the training blocks. During training blocks, the square turned gray when there was no difference from baseline or eye artifacts were detected. The feedback color ranged from a highly saturated red over gray to a highly saturated blue with a total of 40 color steps and depended on the actual fm-theta activity. The feedback color was updated every 250 ms and changed to red when the fm-theta power was enhanced, and changed to blue when the power was decreased relative to fm-theta start baseline power. Ninety-five percent of the power range was covered by the feedback saturation scale. Values above 97.5% or below 2.5% were indicated by maximal red or blue saturation, respectively.

DEPENDENT VARIABLES AND STATISTICAL ANALYSES

In accordance with Dempster and Vernon (2009) neurofeedback success was assessed using two different learning indices, each quantifying a potentially distinct aspect of training success. Concretely, the first learning index (L1) captures dynamical changes within neurofeedback sessions and therefore reflects the immediate responsiveness to neurofeedback. For the quantification of L1, training power was extracted for each training block (1–6) and baseline measurement (start, end baseline) and averaged across all training sessions as fm-theta changes relative to the power observed during the first start baseline measurements.

In contrast, the second learning index (L2) focuses on the maintenance of such enhancements from session to session and captures changes over the whole course of training. Therefore, L2 reveals rather lasting training effects. To achieve L2, effects over the course of training were compared to brain activity at the beginning of the training. Frequency changes of each training session were quantified as changes relative to the first training session. Both, L1 and L2 were calculated with respect to changes in μV and show differences between participants belonging to the actual NF group and the pseudo-NF control group (Enriquez-Geppert et al., 2013b).

TRAINING EFFECTS ON FM-THETA FREQUENCY

To test if there were training effects in L1 within sessions compared to the baseline measurements, a repeated-measures ANOVA with the factor *block* (start baseline, block 1, block 2, block 3, block 4, block 5, block 6, end baseline) was calculated for the changes in μV. Concerning the potential increase of fm-theta over the course of training, L2 was analyzed by means of a repeated-measures ANOVA with the factor *session* (one to eight) for changes calculated in μV.

CORRELATION OF EARLY AND FINAL TRAINING SUCCESS

To investigate if early training effects are related to the final training success, a Pearson product-moment correlation was computed for fm-theta changes of the second and the eighth session (after testing for normal distribution by the Kolmogorov-Smirnov Test). The correlation was tested by means of a one-tailed *t*-test for significance using SPSS Statistics 20 (SPSS, Chicago, USA). Learning index L2 was applied.

MULTIPLE REGRESSION ANALYSES FOR PREDICTING TRAINING SUCCESS BY BRAIN STRUCTURE

To investigate whether training success was associated with volumes and concentration measures of gray and white matter ROIs, four different regression analyses were conducted using a stepwise method in order to test which set of variables significantly predicts training success. For each calculation of the learning index (L1, L2) two regression analyses were set up. One regression analyses used gray matter ROIs as predictor variables, the other white matter ROIs (corresponding volume and concentration measurements were entered into one model; see **Table 1**). The regression models were tested for significance using SPSS Statistics 20 (SPSS, Chicago, USA). Standardized beta values (β) and corresponding significance values are reported as well.

RESULTS

FM-THETA INCREASES WITHIN SESSIONS AND ACCUMULATES OVER THE COURSE OF TRAINING

Figure 1 depicts fm-theta changes within sessions across all training days (L1), as well as the alterations over the course of the training (L2). Indeed, a significant amplitude increase can be observed within the neurofeedback sessions relative to the baseline measurements. Similarly, amplitude increases from session to session are highlighted as well. Statistical analyses did confirm these observations. The main effect *block* was significant for the repeated-measures ANOVA testing changes in L1 $[F_{(7,\ 126)} = 18.882,\ p < 0.001]$. The main effect *session* of the repeated-measures ANOVA testing for theta frequency power changes over the course of training (L2), was as well-significant $[F_{(7,\ 126)} = 6.315, p < 0.001]$.

Table 1 | Overview of multiple regression analyses.

Model	Criterion	Significance	β-values	Significant predictor variable
1	L1 in μV	$p < 0.01$	0.63	vol., r. MCC
2	L1 in μV	$P < 0.01$; $p < 0.001$	0.681;0.681	conc., r. cingulate bundle and vol. cingulate bundle
3	L2 in μV	n.s.	/	/
4	L2 in μV	n.s.	/	/

Four regression analyses were conducted on the learning indices L1 and L2 as criterion variables. These criterion variables were predicted on the basis of gray and white matter ROIs (volume and concentration measurements). For each analysis the significance, the standardized β *values, and the significant predictor variables are listed. Abbreviations: vol., volume; conc., concentration; r., right; l., left.*

EARLY NEUROFEEDBACK SUCCESS CORRELATES WITH FINAL TRAINING SUCCESS

As expected, there was a positive and highly significant correlation between training success in the second and eighth session ($r = 607$; $p < 0.01$; see **Figure 1**) for L2. Thus, the final ability to control one's own brain activity after training was positively correlated to initial training success.

PREDICTIONS OF TRAINING SUCCESS FROM BRAIN STRUCTURE

An overview of the results obtained by the multiple regression analyses is presented in **Table 1**. From these data it can be seen that no significant model was revealed when testing L2. However, strong evidence with regression models for dependent variables L1. Therefore, statistics assessing effects on L2 will not be reported.

Predicting L1 from gray matter characteristics: the right MCC predicts fm-theta increase within sessions

A significant model emerged using the stepwise method $[F_{(1,\ 17)} = 11.186,\ p < 0.01$, adjusted $R^2 = 0.361]$ in which the gray matter volume of the right MCC (see **Figure 2**) significantly predicted the gain of dynamical changes ($\beta = 630, p < 0.01$). No other gray matter ROIs were predictive.

Predicting L1 from white matter characteristics: the cingulate bundle predicts fm-theta increase within sessions

Similar effects were also found for the white matter below the midcingulate cortex. Utilizing the stepwise method for white matter ROIs as possible predictor variables for the gain of dynamical changes resulted in a significant model $[F_{(2,\ 16)} = 24.651,\ p < 0.001$, adjusted $R^2 = 724]$. Significant predictors were the concentration within the right cingulate bundle ($\beta = -1.03$, $p < 0.001$) and the volume of the left cingulate bundle ($\beta = 0.681$, $p < 0.001$; see **Figure 3**).

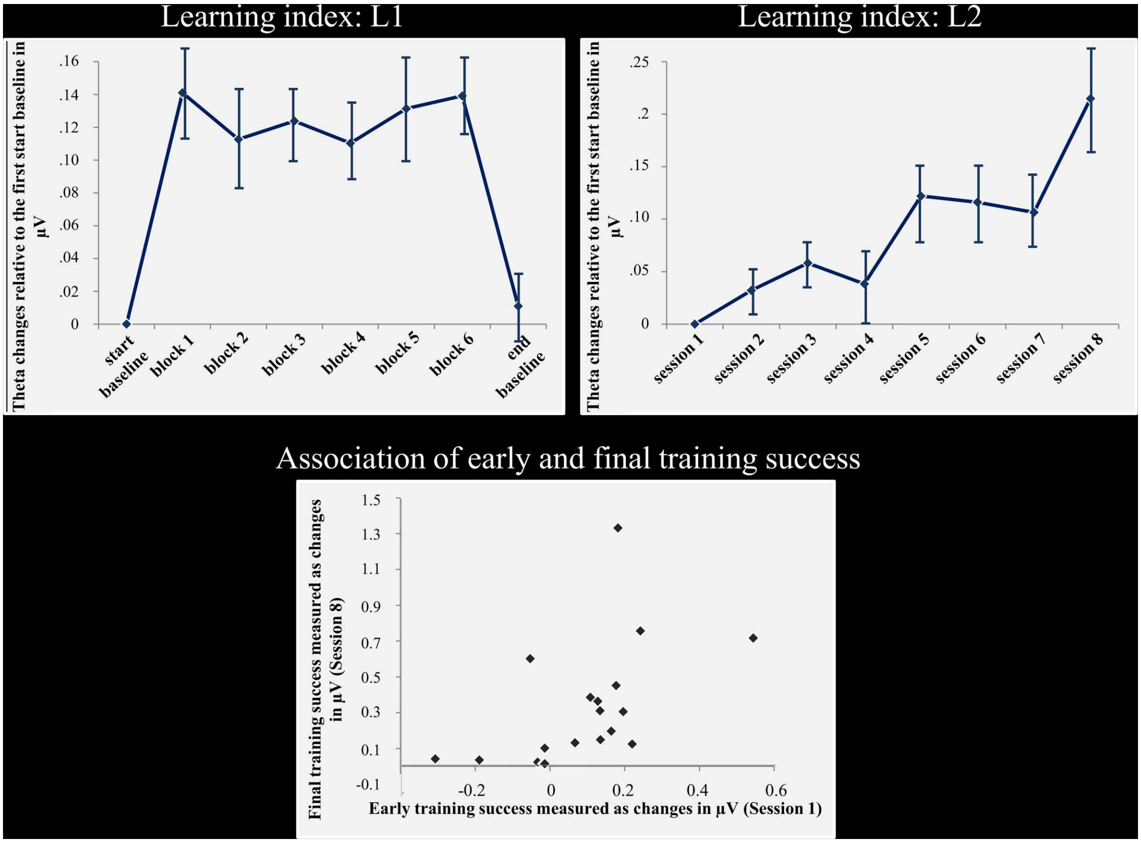

FIGURE 1 | Neurofeedback success and association of early and final training success. Top: the left column shows the fm-theta increase as reflected by the learning L1. This index reflects amplitude changes calculated across all training sessions for the start baseline measurement, blocks 1–6, and the end baseline measurement. During feedback, fm-theta is strongly enhanced compared to the start and end baselines. The right column depicts the fm-theta changes during the course of training, beginning with sessions 1–8. During the course of training, fm-theta enhancements are accumulating with each training session. Means and standard errors of means are depicted. **Bottom:** Training induced fm-theta enhancements are depicted for the second and the eights session for each participant. The figure illustrates the strong relationship of early and final training success. The stronger the fm-theta increase is at the beginning of the training, the better the final training outcome.

DISCUSSION

Neurofeedback has been suggested as a powerful neuroscientific approach to modulate cognition, task performance, and clinical symptoms. Prior studies on neurofeedback revealed substantial inter-individual differences in training success, even reporting non-responders, i.e., participants who are not at all able to modulate their brain activity (e.g., Hanslmayr et al., 2005; Doehnert et al., 2008). One goal of this study was to assess whether early training outcome within an eight-session neurofeedback training study would be correlated with the finally achieved fm-theta enhancement. The results show that already in the second training session the amount of fm-theta enhancement indicates the finally achieved fm-theta augmentation observed at the end of training. Importantly, these data suggest that early training responsiveness serves as predictor for the ultimate training success. These findings are in agreement with observations of Weber et al. (2011), who focused on SMR neurofeedback.

However, from a neuroscientific perspective it is of substantial interest to describe neuronal aspects underlying neurofeedback success. Up until now, nothing has been reported in the literature regarding potential factors contributing to neurofeedback training success. Therefore, this study mainly set out to assess the relationship between preexisting structural differences and the modulation of fm-theta by neurofeedback. It was reasoned that preexisting inter-individual differences in the morphology of brain structures involved in the generation of fm-theta may as well be associated with training success. Hence, volume and concentration measures of gray and white matter ROIs in mid-cingulate and prefrontal regions were used as predictors for neurofeedback training success. Two types of learning indices were chosen. While the first index focuses on the ability to enhance fm-theta within a training session, the second describes the maintenance of enhancements from one training session to the next and thus stresses gradual changes over the whole course of training. Larger volumes of the right MCC, as well as higher white matter concentration of the right and larger volumes of the left cingulate bundle were associated with stronger fm-theta enhancement during training sessions as reflected by the first learning index (L1). However, the ROIs did not predict lasting training success as reflected by L2. Thus, known brain structures acting as

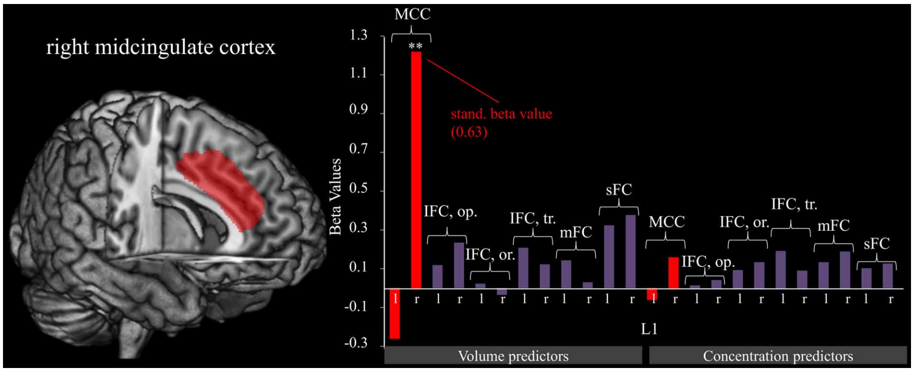

FIGURE 2 | Right midcingulate cortex predicts L1. The graphic shows the relation of fm-theta increases during training sessions (L1). Predictor variables include gray matter volumes (left) and concentrations (right). The figure reveals that the volume of the MCC contributes strongly to training success as is shown by the significant (**$p < 0.001$) beta value, whereas all other brain structures show a negligible relationship. For significant predictors, standardized beta values are included as well.

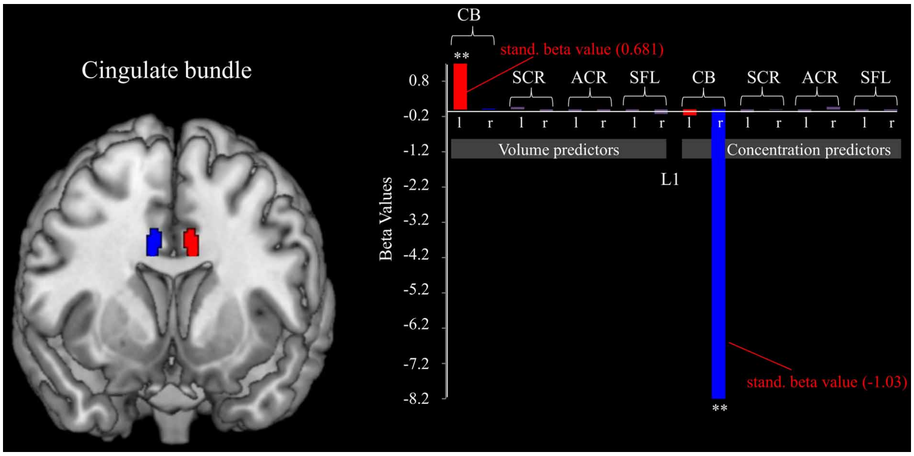

FIGURE 3 | Cingulate bundle morphology predicts L1. The figure shows the relation between the volumes and concentrations of white matter belonging to different brain tracts and the fm-theta increases during training sessions (indexed by L1). The volume of the left, and the concentration of the right cingulate bundle act as significant (**$p < 0.001$) predict variables of the ability to increase fm-theta during training sessions. No further white matter structures influence training success. Standardized beta values are included for the significant predictor variables.

fm-theta generators seem to play only a minor role with respect to L2. Possibly other brain regions involved in learning and memory of operant conditioning may be of more importance regarding the maintenance of training enhancements. Thus, different aspects of neurofeedback training may be associated with morphological differences in diverse functionally specialized brain structures.

With respect to the neurofeedback learning indices, it is important to consider that these were shown to differentiate between the actual neurofeedback group and an active control, the so-called pseudo neurofeedback group. In a previous study we found that the pseudo group showed no enhancement of L1 at all, and significantly weaker non-specific effects in L2 (Enriquez-Geppert et al., 2013a). Importantly, this pseudo protocol led to similar experiences of pseudo subjects concerning commitment, motivation, and task difficulty (Enriquez-Geppert et al., 2013a). Together these findings suggest that the L1-related changes do not simply reflect increased task difficulty due to the use of mental strategies to enhance fm-theta during training.

The observed associations between gray and white matter structure and the enhancement of fm-theta during the actual training sessions were in line with hypotheses based on potential generators of fm-theta. Several studies using intracerebral recordings in animals and humans concluded that fm-theta has its main source in the MCC (Wang et al., 2005; Tsujimoto et al., 2009; Womelsdorf et al., 2010). Also, source localization of scalp-recorded fm-theta in healthy subjects consistently indicates the MCC as major generator (Iramina et al., 1996; Gevins et al., 1997; Asada et al., 1999; Ishii et al., 1999; Onton et al., 2005; Sauseng et al., 2007).

Thus, the association of inter-individual differences of MCC volumes, cingulate bundle volumes, and concentrations with fm-theta responsiveness to training was expected and confirmed. Larger volumes seem to facilitate the possibility to modulate fm-theta oscillations. The reverse suggestion might be that small midcingulate volumes imply reduced success during feedback sessions. Differences in MCC morphology have already been reported in relation to neurofunctioning and performance. Earlier work already indicated that the MCC shows a high degree of structural variability in terms of gray and white matter volumes, local gyrification or regional microstructure (e.g., Yücel et al., 2001; Fornito et al., 2004; Huster et al., 2007, 2009a,b). In general, gyrification has been shown to have a functional significance (Welker, 1990), and to be affected by the underlying cytoarchitecture (e.g., Watson et al., 1993), as well as the neural connectivity (Caviness et al., 1989). Vogt et al. (1995) showed that the variation of the gyral pattern is associated with differences in the size and distribution of cytoarchitectonically defined regions within the MCC. When present, the PCG comprises area 32′. It has been suggested that the presence of the PCS may be a consequence of stronger internal connectivity within this area, whereas the absence may be related to stronger external connectivity (Welker, 1990). The degree of midcingulate fissurization was demonstrated to relate to differences in behavior, as well as to neuropsychological functioning in executive tasks (Fornito et al., 2004; Huster et al., 2009a,b, 2012). Some of these studies also showed that subjects with a leftward midcingulate folding asymmetry exhibited increased electrophysiological reactivity in tasks calling for cognitive control.

Structure-function associations have also been revealed for micro-structural properties of the white matter utilizing diffusion tensor imaging (DTI) and event related potentials (ERPs). Findings indicate that increased amplitudes of electrophysiological activity coincide with augmented efficiency of brain communication, as for example seen with the ERN, an ERP associated with an erroneous response. The ERN is suggested to reflect theta oscillations and to be generated in the MCC (e.g.,Trujillo and Allen, 2007; Cavanagh et al., 2012). Westlye et al. (2009) investigated inter-individual differences of ERN amplitudes and fractional anisotropy (FA), a measure providing information about white matter microstructure, such as axon caliber, fiber density, or myelination. Interestingly, associations of higher ERN amplitudes and increased FA values were observed in the left cingulate bundle (Westlye et al., 2009). Likewise, Cohen (2011) found higher theta power to be associated with stronger tract connectivity between regions underlying EFs such as the MCC, the striatum, and the ventrolateral frontal cortex. Similarly, measures indexing the transmission of signals across the corpus callosum, as the so-called inter-hemispheric transfer time (IHTT), have been found to be associated to micro-structural properties of the corpus callosum as well. The IHTT is computed by analyzing latency-differences of sensory evoked potentials between contralateral and ipsilateral electrodes when presenting stimuli to only one hemisphere. This way, Westerhausen et al. (2006) showed a negative correlation between the IHTT and the mean diffusivity in the posterior third of the corpus callosum. Likewise, Withford et al. (2011) predicted the IHTT from FA and mean diffusivity.

When analyzing the association of training effects and brain structure, at least two issues arise. In case of the current study, the ability to enhance one's own fm-theta power might be based on larger number of neurons in the MCC. However, from a microscopic perspective ample possible cellular and molecular factors exist that contribute to variations in volume or structural concentrations. Among them are variations in the amount of dendritic or axonal arborization, synaptic connections, vascularization, as well as differences in the number of neurons that all can also lead to differences at the functional level. When finding associations of training success and brain structure, further issues arise. For example, such effects may well be caused by common genetic or environmental enrichment effects on both brain structure and training success. The engagement in physical activities (e.g., Kramer et al., 1999) and the engagement in cognitively challenging events (Hertzog et al., 2009) may serve as examples for environmental effects, both of which have shown to also affect neuroplasticity.

In conclusion, inter-individual differences concerning the ability to change one's own brain states are in focus of current neurofeedback research. By analyzing the associations of training success and pre-existing inter-individual differences in midcingulate morphology, we elucidated putative neuroanatomical foundations for the ability to learn to control one's brain system ultimately causing fm-theta generation.

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Attention and P300-based BCI performance in people with amyotrophic lateral sclerosis

Angela Riccio[1,2]*, Luca Simione[2,3], Francesca Schettini[1,4], Alessia Pizzimenti[5,6], Maurizio Inghilleri[5], Marta Olivetti Belardinelli[2,7], Donatella Mattia[1] and Febo Cincotti[1,4]

[1] *Neuroelectrical Imaging and BCI Laboratory, Fondazione Santa Lucia, Rome, Italy*
[2] *Department of Psychology, Sapienza University of Rome, Rome, Italy*
[3] *CNR, Institute of Cognitive Sciences and Technologies, Rome, Italy*
[4] *DIAG, Sapienza University of Rome, Rome, Italy*
[5] *Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy*
[6] *Crossing Dialogues Association, Rome, Italy*
[7] *Interuniversity Centre for Research on Cognitive Processing in Natural and Artificial Systems (ECONA), Rome, Italy*

Edited by:
Elisabeth V. C. Friedrich, University of Graz, Austria

Reviewed by:
Sonja C. Kleih, University of Würzburg, Germany
Eric W. Sellers, East Tennessee State University, USA

***Correspondence:**
Angela Riccio, Neuroelectrical Imaging and BCI Laboratory, Fondazione Santa Lucia, Via Ardeatina, 306, 00179 Rome, Italy
e-mail: a.riccio@hsantalucia.it

The purpose of this study was to investigate the support of attentional and memory processes in controlling a P300-based brain-computer interface (BCI) in people with amyotrophic lateral sclerosis (ALS). Eight people with ALS performed two behavioral tasks: (i) a rapid serial visual presentation (RSVP) task, screening the temporal filtering capacity and the speed of the update of the attentive filter, and (ii) a change detection task, screening the memory capacity and the spatial filtering capacity. The participants were also asked to perform a P300-based BCI spelling task. By using correlation and regression analyses, we found that only the temporal filtering capacity in the RSVP task was a predictor of both the P300-based BCI accuracy and of the amplitude of the P300 elicited performing the BCI task. We concluded that the ability to keep the attentional filter active during the selection of a target influences performance in BCI control.

Keywords: brain computer interface, amyotrophic lateral sclerosis, P300, attention, working memory

INTRODUCTION

Brain computer interface (BCI) exploits neurophysiological signals to control external devices for a range of applications (Wolpaw and Wolpaw, 2012) such as communication, environmental control, movement control and motor rehabilitation. In the last years the scientific community has made substantial efforts to bring usable BCIs for communication from the laboratory to severely disabled users' home (Sellers et al., 2010). Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing progressive physical disabilities due to the affection of motor nervous system. This generally leads to death from respiratory failure but life can be extended for several years through artificial ventilation. With the advance of the disease people with ALS may become totally paralyzed and be effectively "locked in" (Oliveira and Pereira, 2009).

Because of the motor characteristics of the disease at the ultimate stage, people with ALS are considered as potential users for the BCI for communication. Studies on BCIs controlled by people with ALS were conducted (Sellers and Donchin, 2006; Hoffmann et al., 2008; Nijboer et al., 2008). The possibility of a long-term independent home use for severely disabled people with ALS was also demonstrated in a single-case report (Sellers et al., 2010). Home based BCI use significantly contributed to quality of life and productivity of the user.

P300-BASED BCIs

Among electroencephalographic (EEG) features utilized as input to control a BCI, the Event Related Potentials (ERPs) are transient electric potential shifts time locked to an external event. Such EEG modulations reflect various aspects of cognitive processing. In a typical ERP-based BCI paradigm an adapted oddball task (Fabiani et al., 2007) is implemented. The standard oddball paradigm consists of the presentation of a deviant stimulus in a stream of standard stimuli, the former eliciting the P300 component.

The P300 is a positive deflection typically appearing about 300 ms after the stimulus presentation serving as a link between stimulus characteristics and attention. Two distinct P300 subcomponents have been characterized, the frontal P3a and the central parietal P3b (Polich, 2007). Along with the term P300 we will refer to the P3b component, which has been proposed to reflect memory storage as well as serving as a link between stimulus characteristics and attention (Näätänen, 1990; Patel and Azzam, 2005).

A BCI system which detects occurrences of the P300 in its input EEG signal is usually referred to as P300-based BCI in the literature. Farwell and Donchin (1988) presented the first visual P300-based BCI paradigm (P300 speller) consisting of a 6 by 6 symbol matrix wherein symbols were arranged within rows and columns. Throughout the course of a trial, rows and columns were serially intensified in a random order. The task of the participants was to focus attention on the desired letter which represented the "rare event" of the oddball paradigm and which elicited the P300. The computer identified the attended item as the intersection of the row and column that elicited the largest P300.

Thereafter, many studies were conducted on the P300 speller (Nijboer et al., 2008; Kleih et al., 2010). Other similar visual P300-based devices have also been developed and investigated with able and not able-bodied participants (Piccione et al., 2006; Sellers and Donchin, 2006; Riccio et al., 2011; Zickler et al., 2011).

Only a few studies investigated the relationship between P300-based BCIs and healthy subjects' physiological and electrophysiological characteristics. Kaufmann et al. (2012) identified a predictor of P300-based BCI performance, with 34 healthy participants, in the resting heart rate variability (HRV), considered as an index of prefrontal inhibition in tasks requiring executive control. In a further study involving a sample of 40 healthy participants, Halder et al. (2013) underlined a correlation between the amplitude of N2 component elicited during an auditory oddball and the performance both at an auditory P300-based BCI and at a visual P300-based BCI. A correlation between amplitude of the late potential (400–600 ms) elicited by the auditory oddball and performance in a visual P300-based BCI was also reported.

Only one study (Mak et al., 2012) investigated the relationship between P300-based BCI and specific features of the EEG in a group of subjects with ALS. Three types of EEG features were identified as predictors of P300-based BCI performance: the root-mean-square amplitude, the negative peak amplitude of the event-related potential to target stimuli and the frequency power in the theta band.

Specifically there is no knowledge about the cognitive capabilities that influence the ability to control a P300-based BCI. Possible candidates of such capabilities could be found in the selective attention and in the visuo-spatial working memory systems.

P300 RELATIONSHIP WITH ATTENTION AND VISUO-SPATIAL WORKING MEMORY

Attention and working memory are considered as cognitive processes underlying P300 amplitude.

Johnson's (1986) "triarchic model" of the P300 amplitude described many experimental variables affecting P300 amplitude with three general factors: *subjective probability*, *stimulus meaning* and *information transmission*.

The *subjective probability* was considered as an externally determined information and the *stimulus meaning* as an internally determined information. Johnson pointed out that the extent to which this two factors operate depends on the *information transmission*, which can be influenced by two independent variables: an external condition, i.e., *the equivocation*, and an internal condition, i.e., *the attention*.

It was suggested that the P300 is a manifestation of a "context updating" activity occurring when one's model of the environment is revised (Donchin and Coles, 1988). Polich (2003) in the "P300 context-updating model" allocated the process which generates the P300 to an attention driven comparison process by comparing the presented stimulus with the previous event in the working memory. If the stimulus environment is updated, the P300 potential is generated. In a later review, Polich (2007) underlined that selective attention (Kramer et al., 1985) and memory processing (Donchin, 1981) affect P300 amplitude.

Selective attention is defined as the ability to focus our cognitive resources on one relevant aspect of the environment while ignoring irrelevant aspects. The visuo-spatial working memory is defined as the maintenance and or manipulation of task-relevant visuo-spatial information for brief periods of time to guide subsequent behavior.

The concept of attentional filters appeared in literature since the 1950s (Broadbent, 1958). Later, the feature integration theory of attention (Treisman and Gelade, 1980) suggested that we can detect and identify separable features from different objects at an early stage and in parallel, whereas the identification of conjunctions of features (e.g., color and shape) require focal attention to be directed serially to each object location, as a "spotlight".

One popular way to study selective attentional effects is to require subjects to perform a *visual search task*: participants are presented with a visual display comprising a number of items, and they are asked to manually respond if a predefined target is contained in the display (for a review on selective attention see Quinlan, 2003).

In a typical visual search task, stimuli are spatially selected; a task used to investigate the temporal modality of attentional filtering is the Rapid Serial Visual Presentation (RSVP) task. During the RSVP task, stimuli are presented to the participant in the same location on a screen at a rate of 6–20 items/s (Shapiro et al., 1994). The task is to identify one or more targets embedded in the stream of stimuli. A particular condition was found when participants had to report two targets, with a target presented first in the stream (T1) and a second target (T2) presented immediately after. If both targets have to be attentively processed, detection accuracy for the second target (T2) is usually strongly impaired when T2 is presented between 200 and 400 ms after T1. This failure to accurately report T2 has been termed the attentional blink (AB; Raymond et al., 1992). One of the models explaining the AB effect states that the attentional switching between the two targets in a RSVP trial seems to involve an efficient reconfiguration of the filter which analyzes the incoming stimuli (Di Lollo et al., 2005): the filter is initially configured to process T1 and to exclude the distracter items while the central processor gives temporal control signals to maintain the processing. Upon the arrival of the first target the central processor becomes engaged in stimulus processing and response planning: the second target is thus not processed efficiently until the first target has been fully processed and the central processor has re-established endogenous control over the system's configuration. Di Lollo et al. (2005) refer to this as a temporary loss of control. Conversely, T1 may also be masked by T2.

Following Bundesen's (1990) unified theory of visual recognition and attentional selection, perceptual categorizations of elements in the visual field is linked to the limited-capacity of the visual system, i.e., the capacity to filter irrelevant information from a visual scene directly affects the content of the visual working memory. Thus, we can assess the filtering capacity also by using a multi-element array of visual objects presented simultaneously, with a subset of objects indicated as targets and the others as distracters. However, even if the cognitive substrate is similar, as suggested by Bundesen (1990), the attention filtering in a RSVP task operates in a temporal domain whereas in a visuo-spatial working memory task we could assess the capacity to attentionally "filter" distracters in the spatial domain (see Treisman and Gelade, 1980).

A typical visuo-spatial working memory task is the change detection (CD) task, in which participants are presented with an array of one or more items to be remembered after the array is turned off during an interval of seconds. Following this interval a second array is presented and the participant has to judge if it is identical to the first one. Vogel and Machizawa (2004) and Vogel et al. (2005) used this procedure to investigate the electrophysiological basis of visuo-spatial working memory capacity and of the filtering efficiency in controlling access to working memory. Their procedure consisted in two tasks. The first task aimed to investigate the visual memory capacity by presenting an array of 3–4 differently orientated rectangles and requiring the subject to report if, at the second presentation, the rectangles orientation was identical or different from the original. In the second task the subject had to selectively remember only a few relevant items from within an array. The authors found that if the subject was able to efficiently filter the distracters, the electrophysiological substrate modulated by the number of items held in memory (i.e., contralateral delay activity (CDA)) had the same amplitude in the two conditions, with and without distracters (maintaining the same number of relevant items).

Other studies reported that the P300 amplitude was modulated by awareness of the item change in a CD task, with higher amplitude when changes were detected than when changes were not detected (Koivisto and Revonsuo, 2003; Pourtois, 2006).

To investigate the relationship between a range of attentional and working memory processes and the visual P300-based BCI performance, we specifically investigated the temporal dynamics of attention by using a RSVP task (Kranczioch et al., 2007) and the spatial dynamics of attention for visual working memory consolidation by using a CD procedure, as in Vogel et al. (2005).

We hypothesized an association of the parameters reflecting the temporal filtering capacity (RSVP task), the attentive update speed (RSVP task), the memory capacity (CD task) and the spatial filtering capacity (CD task) with the amplitude of the P300 elicited during the P300 speller task and consequently with the P300-based BCI performances.

MATERIALS AND METHODS

PARTICIPANTS

We recruited the participants at the ALS center of the Policlinic "Umberto I" of Rome. From a starting pool of volunteers, we excluded from the study the participants who had previous neurological or psychiatric disorders, degenerative diseases other than ALS, any hindrance in the acquisition of EEG data from the scalp (e.g., wounds, dermatitis), severe concomitant pathologies (fever, infections, metabolic disorders, severe heart failure), episodes of reflex epilepsy. To be involved in the study the volunteers had to have at least one preserved communication channel.

Thus, we included in the study a total of nine volunteers, all naïve to BCI training, (three women; mean age = 59.7 ± 12.3) with definite, probable, or probable with laboratory support ALS diagnosis (mean ALSFRS-R scores: 32.4 ± 8.2; Cedarbaum et al., 1999). Due to the fact that one participant did not perform the behavioral tasks, only the data of eight participants out of nine (three women; mean age = 58 ± 12; mean ALSFRS-R scores: 31.8 ± 8.6) were reported in this article (**Table 1**).

The study was approved by the ethic committee of Fondazione Santa Lucia, Rome and all participants provided an informed consent.

EXPERIMENTAL PROTOCOL

The experimental protocol consisted in two sessions performed on two different days. The first was a BCI session: ALS participants were asked to control a 6 by 6 P300 speller. During the second session the participants were involved in the screening of their attentional filtering efficiency and working memory capacity and were asked to perform two behavioral tasks: a RSVP task (Kranczioch et al., 2007) and the CD task (Vogel et al., 2005).

P300 speller interface

Scalp EEG signals were recorded (g.MOBILAB, g.tec, Austria) from eight channels according to 10–10 standard (Fz, Cz, Pz, Oz, P3, P4, PO7 and PO8; Chatrian et al., 1985; Krusienski et al., 2006) using active electrodes (g.Ladybird, g.tec, Austria). All channels were referenced to the right earlobe and grounded to the left mastoid. The EEG signal was digitized at 256 Hz. Data acquisition and stimuli delivery were managed by the BCI2000 framework (Schalk et al., 2004).

Participants were required to copy spell seven predefined words of five characters each (runs), by controlling a P300 speller (Farwell and Donchin, 1988). The latter consisted of a 6 by 6 matrix containing alphanumeric characters (**Figure 1A**). Rows and columns on the interface were randomly intensified for 125 ms, with an inter stimulus interval (ISI) of 125 ms, yielding a 250 ms lag between the appearance of two stimuli (stimulus onset asynchrony, SOA). For each character selection (trial) all rows and columns were intensified 10 times (stimuli repetitions) thus each single item on the interface was intensified 20 times. Participants were seated facing a 15" computer screen placed at eye level approximately one meter in front of them. The angular distance subtended by the speller was of 15 degrees. A single flash of a letter at the beginning of each trial cued the target to focus. In the first three runs (15 trials in total) EEG data was stored to perform a calibration of the BCI classifier. Thus no feedback was provided to the participant up to this point. A stepwise linear

Table 1 | Demographic and clinical related data of participants (N = 8).

Participants	Age	Sex	ALSFRS-R	Onset
1	56	M	13	Spinal
2	59	M	37	Spinal
3	43	M	33	Spinal
4	75	F	38	Bulbar
5	60	F	34	Bulbar
6	40	M	31	Spinal
7	61	M	28	Bulbar
8	72	F	41	Bulbar

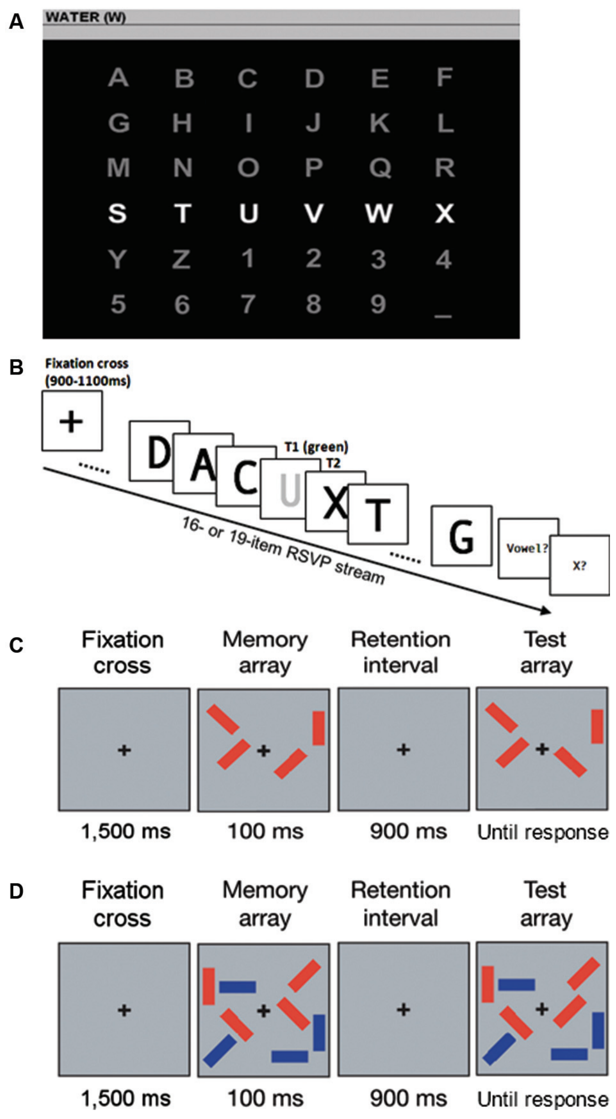

FIGURE 1 | Tasks presented to participants. **(A)** P300 speller interface. **(B)** RSVP task: T1 is the letter "U" (presented in green); T2 (X) follows T1 with no intervening distracter (lag 1). **(C)** CD *baseline task*: In the test array, one of the four items changes orientation. **(D)** *Selection task* of the CD task: the participant is asked to focus on the red items ignoring the blue items. In the test array, one of the four red items changes orientation.

discriminant analysis (SWLDA) was applied to the data from the three calibration runs (i.e., runs 1–3) to determine the classifier weights (i.e., classifier coefficients) (Krusienski et al., 2006). These weights were then applied during the subsequent four testing runs (i.e., testing set; runs 4–7) when participants were provided with feedback. EEG potentials between 0 and 800 ms after each stimulus onset were decimated by replacing each sequence of 12 samples with their mean value and used for the analysis. The next four runs (20 trials in total) characterized a testing phase in which feedback was provided by showing each spelled character. In cases of error the feedback was represented by a dot (instead of the wrongly typed character) to minimize frustration of the participants.

Rapid Serial Visual Presentation task

Temporal attention capabilities of participants were assessed by using the RSVP task as in Kranczioch et al. (2007). In the RSVP task (**Figure 1B**), two targets were embedded in a stream of distracter stimuli. Each stream included 16 or 19 items, of which one or two were targets. All stimuli were presented at central fixation on a monitor with a white background at a presentation rate of 10 Hz. Each letter subtended a region on the screen of about 1.5° × 1.38° of visual angle. Distracters were black capital consonants (except F, K, Q, X, Z) and the distracter sequence was pseudo-randomly extracted, with the constraint that the same letter could not be presented within three sequential positions. The first target (T1) was a green letter, which could either be a vowel or a consonant (except F, K, Q, X, Z), and the second target (T2) was a black capital "X". Each trial started with the presentation of a fixation cross for 900 to 1100 ms (mean 1000 ms). T1 was presented randomly as 4th, 5th, 6th or 7th item in the stream. In 20% of trials T2 was not presented, whereas it followed with no (lag 1), one (lag 2), three (lag 4) or five (lag 6) intervening distracters, in 20% of trials for each condition. After the end of the stimulus stream, two successive screens appeared asking whether the green letter (T1) was a vowel and whether the black X (T2) was contained in the stimulus stream, as in Kranczioch et al. (2005, 2007). Participants completed 20 practice trials before completing 160 experimental trials, presented in a randomized order (32 trials for each of the five conditions).

Due to the motor disabilities of the participants, they were asked to give a binary response (yes or no) to the operator with the residual communication channel.

Change Detection task

Memory capacity and spatial filtering capacity were screened by using a CD procedure. The participants completed two CD tasks (a *baseline* task and a *selection* task). In both tasks, all stimuli were presented on a gray background and each trial started with a fixation cross, presented for 1500 ms at the center of the screen. An array of rectangles (memory array) with varying orientation to memorize was then presented for 100 ms. Each memory array included between three and eight colored rectangles (each subtending a region of about 0.4° × 1.7° visual degrees) presented within a 9.8° × 7.3° region on the screen. Stimulus positions were randomized on each trial, with the constraint that the distance between objects was at least 2° (center to center). Each rectangle was either blue or red and had one of four possible orientations (vertical, horizontal, left 45° and right 45°) randomly chose. The memory array was followed by a retention interval of 900 ms and then by a second array of rectangles (test array). The test array could either be identical to the original memory array or different by, in orientation to one of the previously presented rectangles.

In the *baseline task* (**Figure 1C**), each memory array consisted of three or four rectangles of the same color (all blue or all red), with one out of four possible orientations (vertical, horizontal and two diagonals) randomly extracted. The participants were asked to report if the orientation of the rectangles in the test array was identical to the ones in the memory array. The task included 10 practice trials and 40 experimental trials for condition, for a total of 80 trials, fully randomized in a unique block.

In the *selection task* (**Figure 1D**), each memory array consisted of six or eight rectangles. Half of the rectangles were blue and the other half were red. Half of the participants were instructed to memorize the blue rectangles, considered as targets, and to ignore the red rectangles. They were asked thus to report if the orientation of the blue rectangles in the test array was identical to the ones in the memory array. Half of the participants were instructed to memorize the red rectangles, considered as targets, and to ignore the blue ones. In this case they were asked to report if the orientation of the red rectangles in the test array was identical to the ones in the memory array. This task included 10 practice trials and 40 experimental trials for condition, for a total of 80 trials, fully randomized in a unique block.

Due to the motor disabilities of the participants, they were asked to give a binary response (yes or no) to the operator with the residual communication channel.

DATA ANALYSIS

P300 morphology

EEG data was high pass and low pass filtered with cut off frequencies of 0.1 Hz and 10 Hz respectively using a 4th order Butterworth filter. In addition, a notch filter was used to remove 50 Hz contamination due to the AC interference. Data was divided into 1000 ms long epochs starting with the onset of each stimulus. Epochs in which peak amplitude was higher than 70 μV or lower than −70 μV were identified as artifacts and removed. A baseline correction was done based on the average EEG activity within 200 ms immediately preceding each epoch. The average waveform for both target and non-target epochs was computed for each trial in order to assess P300 peak amplitude. Particularly, amplitude of the P300 potential in Cz was defined as the highest value of the difference between target and non-target average waveforms in the time interval 250–700 ms (P300 amp, **Figure 2**).

Single trial classification

To provide an estimate of the classifier accuracy we considered the binary classification problem target vs. non-target (Blankertz et al., 2011) that takes into account the correct classification of a target or of a non-target. Frequency filtering, data segmentation and artifact rejection were conducted as in P300 morphology section. EEG data were then resampled by replacing each sequence of 12 samples with their mean value, yielding 17 × 8 samples per epoch (eight being the number of channels), which were concatenated in a feature vector (Krusienski et al., 2006). A seven-fold cross-validation was used to evaluate the binary accuracy (BA) of the classifier on each participant's dataset. For each iteration we applied a SWLDA on the testing dataset (consisting

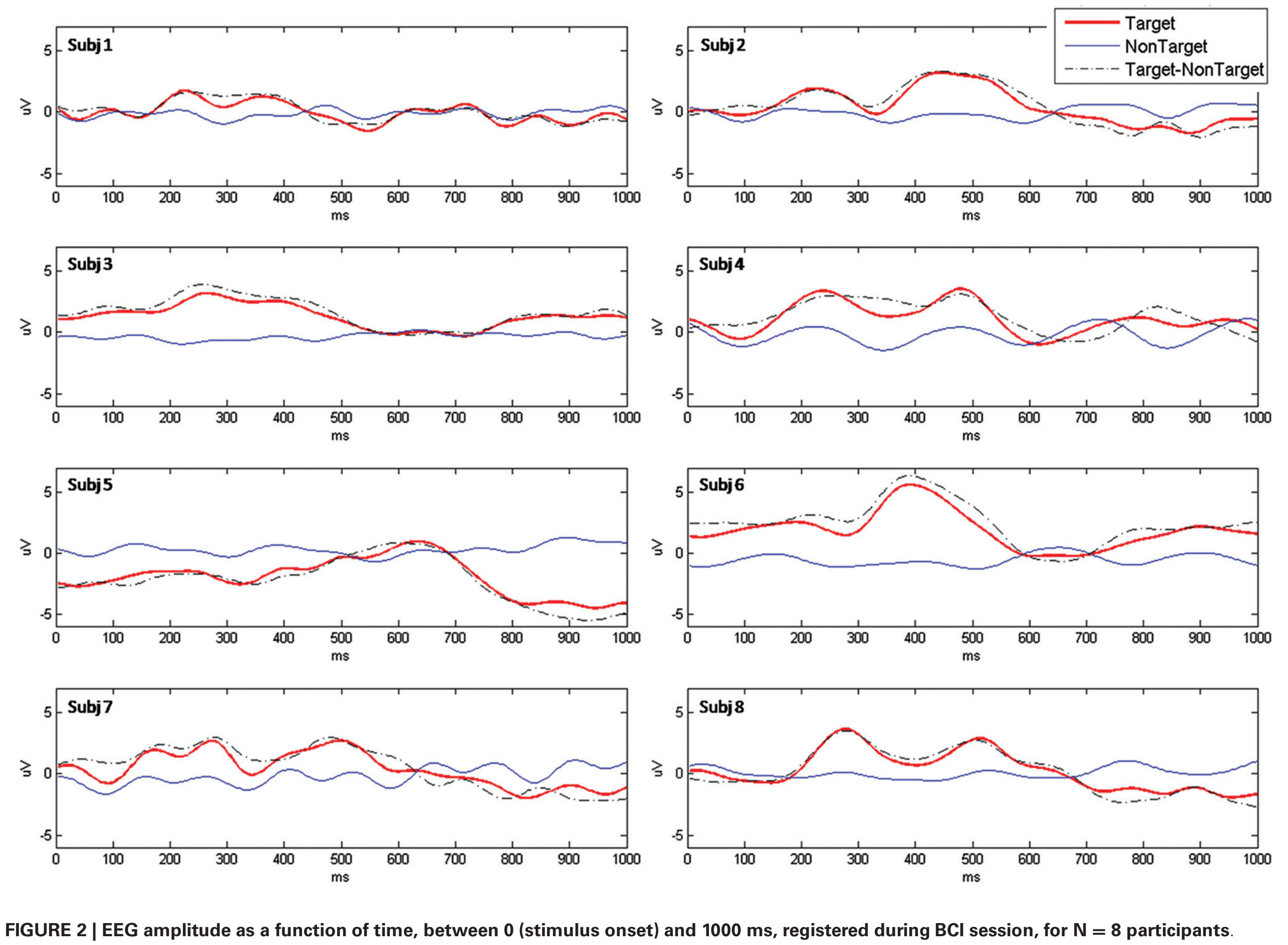

FIGURE 2 | EEG amplitude as a function of time, between 0 (stimulus onset) and 1000 ms, registered during BCI session, for N = 8 participants.

of six words) to extract the 60 most significant control features (Draper and Smith, 1998) and we assessed the BA on the training dataset (the remaining word).

BEHAVIORAL DATA ANALYSIS

The detection accuracy of T1 (T1%) in the RSVP task was considered as an index of the temporal attentional filtering capacity of the participants. Since the detection accuracy of T2 (T2%) was considered as an index of the capability to adequately update the attentive filter, only trials in which T1 had been correctly identified were selected in order to determine T2%.

To investigate the memory capacity we only considered memory arrays with the highest number of rectangles (4 or 8). According to Cowan (2001), we defined the number of items held in memory (K) as $K = S(H-F)$, where S is the size of the array (highest number of item to memorize, $S = 4$), H is the observed hit rate and F is the false alarm rate. We calculated the K index for the *baseline task* (K_b) and for the *selection task* (K_s). To screen for the *attentional spatial filtering capacity* (α) of the participants we subtracted the K_s from the K_b ($\alpha = K_b - K_s$).

STATISTICAL ANALYSIS

Statistical analysis was aimed to test the hypothesis that attentional and memory substrates influence the performance in the P300 speller task and the features of the P300 elicited while performing this task.

Since T1%, T2%, BA, and P3 amp were normally distributed, the Pearson's correlation coefficient of T1%, T2% with the BA and the P3 amp was computed.

Since K_b and α violated the assumption of normality, they were correlated with BA and P3 amp by means of the non-parametric Spearman's correlation test.

For the parameters whose correlation was statistically significant we performed two regression analyses in which attentional parameter (T1%) was considered as the independent variable and BA and P300 amp were considered as dependent variables.

RESULTS

One participant (participant 8) was excluded from the analysis regarding the RSVP task, due to technical problems encountered during data recording. However, that participant's data collected during the CD task were considered in the analysis. One participant did not perform the *selection task* of the CD task because of eye fatigability (participant 5); this lack of data did not allow us to calculate and consider in the analysis her *attentional spatial filtering capacity* (α). One participant (participant 2) refused to perform both the CD tasks (*baseline task* and *selection task*) due to fatigue.

In brief, analysis on the scores collected by means of the RSVP task (T1% and T2%) were performed on seven participants. Analysis on the scores collected by means of the CD task (K_b and K_a), were performed on seven participants when considering the K_b scores, and six participants when considering the K_a scores.

Mean online accuracy in performing the BCI task was 97.5% (SD = 3.8, range = 90–100%, N = 8; **Table 2**), the offline BA was on average of 87.4% (SD = 2.4%, range = 84.5–92.3%, N = 8; **Table 2**). The mean amplitude for P300 amp in Cz, was 3.3 μV (SD = 1.6, range = 1.1–6.5 μV, N = 8).

In the RSVP task, mean accuracy of detection for T1 was 77.2% (SD = 10.4%, range = 65–96.25%, N = 7) and for T2 67.7% (SD = 14.1%, range = 50.3–87.1%, N = 7).

A significant positive correlation was observed between T1% and the offline BA ($r = 0.79$, $p < 0.05$), showing that participants with higher T1% had a higher accuracy in the offline binary classification. To estimate the predictive value of T1% on the BA we computed a regression analysis which resulted in an $F = 8.34$ with a $p < 0.05$, indicating that the variance of the binary performance is predictable by the participant temporal filtering capacity, with $\beta = 0.79$.

A significant positive correlation was found between T1% and P300 amp in Cz (in $r = 0.84$, $p < 0.05$) showing that participants with higher T1% had a larger P300 amp in Cz. As a result of the linear regression, T1 accuracy was significantly predictive of P300 amp in Cz ($F = 16{,}23$ with a $p < 0.05$) with $\beta = 0.87$.

No significant correlation was found between T2%, the offline binary performance and P300 amp in Cz.

The number of items held in memory by the participants (K_b) in the CD task was on average 2.3 items (SD = 0.9, range = 1–3.2, N = 7). The α value was on average 0.6 (SD = 0.5, range = 0–1, N = 7).

Table 2 | Participants' scores with means and Standard Deviations (SD).

Participants	T1%	T2%	P300 amp	K_b	α	BA%	Online acc %
1	69.4	60.8	1.90	3.2	0.2	84.5	95
2	73.7	77.3	2.45	–	–	86.3	100
3	73.7	77.9	4.40	3.2	1.4	87.2	90
4	77.5	50.4	3.45	1.0	1.0	85.9	100
5	65.0	51.3	1.09	2.2	–	86.2	95
6	96.2	87.1	6.55	3.2	0.0	88.6	100
7	85.0	69.3	3.26	1.6	0.4	88.6	100
8	–	–	3.18	1.6	1.0	92.3	100
Mean ± SD	77.2 ± 10.4	67.7 ± 14.1	3.3 ± 1.6	2.3 ± 0.9	0.6 ± 0.5	87.4 ± 2.4	97.5 ± 3.8

T1%: accuracy in detection of T1 in the RSVP task; T2%: accuracy in detecting T2, if T1 is correctly detected, in RSVP task; P300 amp: amplitude of the difference between the P300 elicited by the target and the P300 elicited by the non-target in Cz (P300 speller task); K_b*: K index (number of items held in memory) for the baseline task;* α*: spatial filtering capacity (*$K_b - K_s$*);* BA*%: offline* BA*; Online acc %: online accuracy in P300 speller task*

No significant correlation occurred between K_b, α and the two BCI variables (BA and P300 amp).

DISCUSSION

The purpose of this study was to investigate whether attentive and memory capacities may influence and predict performances in controlling a visual P300-based BCI in a group of people with ALS. We hypothesized that the capabilities of maintaining temporal attentional filters and creating spatial attentional filters would be important cognitive substrates supporting the skill required to operate a visual P300-based BCI.

We found that T1% (RSVP task) was a predictor of the amplitude difference between the P300 elicited by target and the P300 elicited by the non-target in the BCI task. T1% was also found to be a predictor of the offline BA obtained in the BCI task. We considered T1% an index of the capacity of detecting and reporting a target within a stream of distracter stimuli.

We did not find any association between the detection of T2% (RSVP task) and the BCI related variables. No association was highlighted between BCI variables and participants' memory capacity and spatial attention filtering capacity.

RSVP TASK AND BCI TASK

The detection rate of T1 in the RSVP task can be interpreted as an index of selective attention: it represents indeed the capacity to detect a target within a stream of stimuli, to create a memory trace and to retain it. More precisely it represents the basic capability to temporally filter the target by distracters and to maintain the filter in a range of time, keeping a continuous top-down control (Di Lollo et al., 2005). Such capability varies from subject to subject and we demonstrated that it influences the performances in the BCI task, supporting our hypothesis about the existence of a common cognitive substrate between the two investigated tasks.

As the accuracy of detecting T2 is an index of the speed of attentive update, the missed correlation with the considered BCI variables leads us to speculate that the capacity of dynamically update the attentive filter is less likely to be a cognitive substrate supporting the BCI control. This might be explainable by the nature of P300 speller stimulation: the letter stimuli are statically presented on the screen and the central processor does not need to update the filtering map in order to process the successive stimuli. In the RSVP task indeed, a filtering map is configured for the processing of the T1, a green letter, and has to be dynamically reallocated in order to process the T2. Such dynamic reallocation is not a cognitive substrate supporting the target stimuli processing during the P300 speller task. Thus, an association between the T2% and the accuracy in a BCI task could possibly arise by using a speller in which the pattern of the letters is randomized every three to five sequences, stressing the capacity of participants to reallocate their attentional filter.

Although the sample of participants of the presented study had relatively high-motor functioning, the accuracy of detection of T1 (77.6%) in the RSVP task was lower compared with the scores reported in the RSVP literature. Kranczioch et al. (2005), exploiting the same RSVP paradigm utilized in this study, reported accuracy in T1 detection always above 96.5%. It can be argued that the sample involved in Kranczioch et al. (2005) study, was younger (age 19–34) than the sample involved in our study (age 40–72). Interestingly Georgiou-Karistianis et al. (2007) performed a study about the progressive age-related changing in RSVP task performance (sample ranging in age from 18–82; mean age = 42.51 ± 19.21), showing that age was not associated with a reduced ability to detect T1. The accuracy of T1 detection was indeed of 92% on average. In conclusion we can speculate that the capability to temporally filter a target and to maintain it is weaker in our sample of ALS participants in comparison with the healthy samples reported in others studies investigating performances in RSVP task.

CD TASK AND BCI TASK

We hypothesized that the memory capacity and the spatial filtering capacity were associated with the amplitude of the P300 elicited during a P300 speller task and the capability of the participants to control the P300 speller. The lack of relationship between BCI parameters and the variables measured with the CD task did not confirm this hypothesis. According to the Bundesen's (1990) unified theory of visual recognition and attentional selection, the selection of stimuli to be stored in memory is spatial and feature based. We can speculate that the allocation of attention on the selected item during the BCI task is not based on spatial (being the location of the target letter static) or feature characteristics but on symbolic aspects (e.g., semantic aspects of the target letter).

CONCLUSIONS

We can conclude that the cognitive process which influences the performance in BCI control is not the capability to create an attentive map itself, but to keep it active. Following the Huang and Pashler's (2007) Boolean Map Theory of visual attention, the attentional filter is achieved by a boolean map, a mechanism of visual access (spatial filter) that divides the visual field into selected and unselected subfields. A top down mechanism creates and maintains over time the Boolean maps. Such top-down mechanism is crucial to control a BCI speller task, allowing the user to set up and maintain the proper attentional map throughout a trial and thus to select the desired letter.

The data reported in the present paper partly clarify the cognitive substrate related to BCI control in people with ALS. This issue could allow future speculations on the factors underlying BCI control failure observed in potential user groups. The awareness about the processes and the clinical features of BCI potential end-users influencing the BCI performance and use, would allow developing flexible systems, adaptable to different clinical profiles. As also suggested by Schreuder et al. (2013), thus we consider crucial to adapt BCI-based devices to end users with a range of cognitive profiles.

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On ERPs detection in disorders of consciousness rehabilitation

Monica Risetti[1]*, Rita Formisano[2], Jlenia Toppi[1,3], Lucia R. Quitadamo[1,4], Luigi Bianchi[5], Laura Astolfi[1,3], Febo Cincotti[1,3] and Donatella Mattia[1]

[1] Neuroelectrical Imaging and BCI Laboratory, Fondazione Santa Lucia, Rome, Italy
[2] Post-Coma Unit, Fondazione Santa Lucia, Rome, Italy
[3] Department of Computer, Control, and Management Engineering, Sapienza University, Rome, Italy
[4] Department of Electronic Engineering, "Tor Vergata" University, Rome, Italy
[5] Department of Civil Engineering and Computer Science Engineering, "Tor Vergata" University, Rome, Italy

Edited by:
Guilherme Wood, Karl-Franzens-University of Graz, Austria

Reviewed by:
Sonja C. Kleih, University of Würzburg, Germany
Boris Kotchoubey, University of Tübingen, Germany

***Correspondence:**
Monica Risetti, Neuroelectrical Imaging and BCI Laboratory, Fondazione Santa Lucia, Via Ardeatina, 306, 00179 Roma, Italy
e-mail: m.risetti@hsantalucia.it

Disorders of Consciousness (DOC) like Vegetative State (VS), and Minimally Conscious State (MCS) are clinical conditions characterized by the absence or intermittent behavioral responsiveness. A neurophysiological monitoring of parameters like Event-Related Potentials (ERPs) could be a first step to follow-up the clinical evolution of these patients during their rehabilitation phase. Eleven patients diagnosed as VS ($n = 8$) and MCS ($n = 3$) by means of the JFK Coma Recovery Scale Revised (CRS-R) underwent scalp EEG recordings during the delivery of a 3-stimuli auditory *oddball* paradigm, which included standard, deviant tones and the subject own name (SON) presented as a *novel* stimulus, administered under passive and active conditions. Four patients who showed a change in their clinical status as detected by means of the CRS-R (i.e., moved from VS to MCS), were subjected to a second EEG recording session. All patients, but one (anoxic etiology), showed ERP components such as mismatch negativity (MMN) and novelty P300 (nP3) under passive condition. When patients were asked to count the *novel* stimuli (active condition), the nP3 component displayed a significant increase in amplitude ($p = 0.009$) and a wider topographical distribution with respect to the passive listening, only in MCS. In 2 out of the 4 patients who underwent a second recording session consistently with their transition from VS to MCS, the nP3 component elicited by passive listening of SON stimuli revealed a significant amplitude increment ($p < 0.05$). Most relevant, the amplitude of the nP3 component in the active condition, acquired in each patient and in all recording sessions, displayed a significant positive correlation with the total scores ($p = 0.004$) and with the auditory sub-scores ($p < 0.00001$) of the CRS-R administered before each EEG recording. As such, the present findings corroborate the value of ERPs monitoring in DOC patients to investigate residual *unconscious and conscious* cognitive function.

Keywords: acquired brain injury, consciousness, vegetative state, minimally conscious state, ERP, P300, CRS-R

INTRODUCTION

Disorders of Consciousness (DOC), such as Vegetative State (VS), and Minimally Conscious State (MCS) can be the consequence of severe acquired brain injury (such as traumatic brain injury, cerebral anoxia, stroke, toxic brain lesions, and encephalitis) and they usually follow a period of coma (Bernat, 2006; Goldfine and Schiff, 2011). During clinical assessment, patients with DOC typically display the absence or the inconsistency of overt behavioral responses to external stimulation. This unresponsiveness leads to consider them as lacking awareness of themselves and their environment. This approach based on negative evidence might, however, lead to a not negligible rate of diagnostic errors (Andrews et al., 1996; Schnakers et al., 2009a; Cruse et al., 2011).

Recently, the application of neuroimaging techniques such as functional magnetic resonance imaging to DOC patients with a lack of- or minimal responsiveness has provided a promising means for detecting "residual" conscious awareness otherwise not revealed by means of standard clinical approaches (Owen et al., 2006; Owen and Coleman, 2008; Monti et al., 2010; Laureys and Schiff, 2012). Alongside behavioral assessment and functional neuroimaging approaches, the electroencephalographic (EEG) technique has been shown to increase the probability to unveil possible residual covert awareness in each of these patients, with the advantage of an extreme versatile and affordable technique (Babiloni et al., 2009; Cruse et al., 2011; Goldfine et al., 2011; Cruse et al., 2012). To what extent the EEG activity changes in response to several paradigms applied to DOC patients (especially those in VS) allow to unambiguously establish covert awareness, still remains a matter of debate (Goldfine et al., 2012).

In the wide spectrum of the EEG brain signals, event-related potentials (ERPs) are recognized as a cornerstone to assess information processing ability in the absence of explicit behavior (Donchin et al., 1978; Vanhaudenhuyse et al., 2008; Lehembre et al., 2012). Despite the clinical and prognostic significance of

ERP presence being currently under definition, the elicitation of such EEG brain responses is an effective sign to immediately identify patients who are responsive on a cortical level. In particular, the presence of long-latency ERP components, involving fronto-temporo-parietal cortices and backward connection between these areas, has been described as a reliable marker for neuronal conscious perception (Del Cul et al., 2007; Garrido et al., 2007; Boly et al., 2011). The elicitation of ERP after brain injury can also help predict the subsequent recovery of consciousness and, if systematically assessed, can suggest new rehabilitation strategies (Steppacher et al., 2013).

In the light of these considerations, the aims of this study were to monitor auditory ERP's components detected in a group of DOC patients during their rehabilitative treatment, and ultimately to correlate ERP components with the outcome of the clinical assessment performed by means of the gold-standard JFK Coma Recovery Scale Revised (CRS-R) (Kalmar and Giacino, 2005; Lombardi et al., 2007). The relevance of this longitudinal pilot study resides in fostering the introduction of a quantifiable measure to assess patients' motor-independent responses to commands during their rehabilitation treatment.

We administered an auditory paradigm to elicit ERP components such as P300 (Sutton et al., 1965; Squires et al., 1975; Friedman et al., 2001) and the mismatch negativity (MMN) (Näätänen et al., 1978; Tiitinen et al., 1994; Boly et al., 2011). These cognitive ERP components offer the opportunity to explore the patient's automatic attentional (pre-attentive) and attentive resources through the easiest accessible sensory modality. To this purpose, we chose a 3-stimuli *oddball* paradigm composed by standard, deviant tones and also the subject own name (SON), this latter being introduced as a novel stimulus (Holeckova et al., 2006; Perrin et al., 2006; Fischer et al., 2008, 2010; Qin et al., 2008). Such SON stimulus seems to amplify the response normally elicited by novel simple tones (less frequent than deviants), likely being characterized by a greater acoustic complexity (Kotchoubey et al., 2004) associated with a strong semantic/ecological salience (Perrin et al., 2006). Although it should be considered that the response elicited by SON stimuli in DOC patients is not name-specific, there is repeated evidence of a robust P300 when the subjects were asked to count the own name and thus, it still remains a valuable instrument to probe possible signs of residual "command-following" in these patients (Schnakers et al., 2008, 2009b; Lehembre et al., 2012).

Understanding to what extent changes in clinical indices (CRS-R subscales scores) observed during rehabilitation may have a counter part in the neurophysiological parameters would facilitate the elaboration of an integrated protocol for the assessment of patients with DOC. In addition, monitoring such electrophysiological brain responses represents the initial step to unmask relevant EEG activity required to use an EEG-based Brain Computer Interface (BCI) as a tool for a basic form of communication (Wolpaw et al., 2002).

MATERIALS AND METHODS

PATIENTS

Sixteen patients were consecutively recruited at the Post-Coma Unit of the Neurorehabilitation Hospital "Fondazione Santa Lucia" (Rome) at the time of admission. We excluded one patient with bilaterally absent Brainstem Auditory Evoked Responses (BAERs, see paragraph EEG data acquisition), and four patients from whom we could not acquire a usable EEG-signal, due to decompressive craniectomy, vegetative dysauthonomia (profuse sweating) and psychomotor agitation. All 11 patients enrolled in the study had a history of severe acquired brain injury (Glasgow Coma Scale = 8 in the acute phase; Teasdale and Jennett, 1974; Jennett et al., 1976) and met the CRS-R diagnosis of VS and MCS. The CRS-R is a standardized and validated behavioral assessment scale to determine the patients' level of consciousness. It assesses auditory, visual, verbal and motor function as well as communication and arousal level, with a total score ranging between 0 (coma) and 23 (emergence from MCS). Patients' demographic, clinical and CRS-R sub-scores are reported in **Table 1**. Four out of 7 patients (patients 2, 7, 8, 11 in **Table 1**) underwent a second EEG

Table 1 | Demographic and clinical data of the study sample of Vegetative State (VS) and Minimally Conscious State (MCS) patients.

Patient	Gender	Age	Etiology	Months from event	CRS-r sub-scores	Diagnosis
1	Male	30	Traumatic Brain injury	13	3–3–2–0–0–2	MCS
2	Female	21	Traumatic Brain injury	12 16	2–1–2–2–0–1 4–2–3–1–0–2*	VS MCS
3	Male	50	Ischemic stroke	3	1–0–0–0–0–2	VS
4	Male	43	Hemorrhagic stroke	19,5	3–4–4–2–1–2	MCS
5	Female	45	Hemorrhagic stroke	15	1–1–2–0–0–2	VS
6	Male	25	Hemorrhagic stroke	5	1–1–2–1–0–2	VS
7	Female	50	Cerebral Anoxia	5 8	1–1–2–2–0–2 3–1–4–3–1–2*	VS MCS
8	Male	22	Traumatic Brain injury	4 4,5	2–1–1–1–0–2 4–5–5–2–1–2 *	VS MCS
9	Male	52	Hemorrhagic stroke	4	1–0–2–1–0–1	VS
10	Female	63	Ischemic stroke	10,5	4–5–5–2–1–2	MCS
11	Female	20	Traumatic Brain injury	4 6	1–1–2–0–0–2 3–3–3–0–1–2*	VS MCS

Asterisks indicate the CRS-R scores relative to the second evaluation session, performed in patient 2, 7, 8, and 11.

recording session at the time of a detectable evolution from VS to MCS, according to the daily clinical assessment (i.e., CRS-R).

The study was approved by the Independent Ethics Committee of the Fondazione Santa Lucia and was conducted in accordance with the Declaration of Helsinki guidelines. We obtained written informed consent from all patients' legal representatives and medical teams.

EEG DATA ACQUISITION

BAERs and auditory Event Related Potentials (ERPs) were recorded in the Post-Coma Unit at patients' bedside, as part of the routine evaluation of admitted patients. The CRS-R was administered prior to each EEG recording.

We applied an auditory *Oddball* paradigm (Sutton et al., 1965) which included standards, deviants and the SON, digitally recorded by a female speaker using Adobe Audition software, considered as a *novel stimulus* (Fischer et al., 2008). The standard and deviant stimuli were tone bursts of 800 Hz and 1 KHz, lasting 30 ms for the standards and 75 ms for the deviants. Auditory stimuli were delivered binaurally by means of inserted earphones at an intensity of 75 dB HL. Patients were presented with 6 blocks. Each block was composed by 500 stimuli, specifically: 415 standards, 70 deviants, and 15 novel stimuli. Stimuli were pseudo-randomly presented: each deviant was preceded by 5/6 standards and between two novel stimuli there were at least 4/5 deviant stimuli. Stimulus onset asynchrony (SOA) was 600 ms for standard and deviant stimuli, whereas the standard tone burst following a novel stimulus (SON) was presented 1500 ms after the onset of the novel stimulus (duration from 350 to 450 ms). Such SOA duration was chosen in order to allow the subject to listen to the complete own name whose duration was longer than the other standard and deviant tones (**Figure 1**).

Stimuli sequences were programmed and delivered through the BCI2000 Software (www.bci2000.org). Two recording conditions were considered: passive where patients were asked to listen to the auditory stimuli, and active condition where they were verbally instructed to count the novel stimuli (i.e., their own name). The active blocks were always preceded by the passive, to avoid patients to persist with the counting task even when not requested.

Prior to administration of the auditory stimuli, 5 min of EEG signal were acquired (eyes-closed baseline condition) to estimate the Individual Alpha Frequency (IAF) peak, defined as the frequency associated to the strongest EEG power peak in alpha frequency range (8–13 Hz), over the posterior electrodes (Klimesch, 1999). The patients were asked to close their eyes and remain as relaxed as possible. Eyelids were maintained closed with help when necessary.

Scalp EEG potentials were continuously recorded from 10 electrode placed according to the 10–20 International System at the following positions: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, Oz (references at earlobes; impedance was kept below 5 KΩ; sampling rate was 1 KHz; Brain Amp/Vision system, Brain Products GmbH, Germany). The electro-oculogram (EOG) was recorded from two pairs of electrodes (one above and below the right eye and the other on the outer canthi of the two eyes), in order to run a semi-automatic procedure for the ocular movement artifacts removal. The patients' level of vigilance was monitored online through recording session by inspecting the EEG traces to detect signs of sleep onset.

EEG DATA ANALYSIS

The EEG data were band pass filtered (1-45 Hz). Eye movement artifacts were removed from recordings based on EOG traces, by means of Gratton-Coles algorithm (Gratton et al., 1983). Other artifacts were detected with a semi-automatic procedure based on two different criteria: threshold criterion (traces which exceeded a threshold of ±80 μV were rejected) and gradient criterion (traces in which the difference between two consecutive samples exceeded ±50 μV were rejected). Data were offline filtered between 2 Hz and 20 Hz and baseline corrected in 100 ms before the stimulus onset. Responses to standard and deviant stimuli

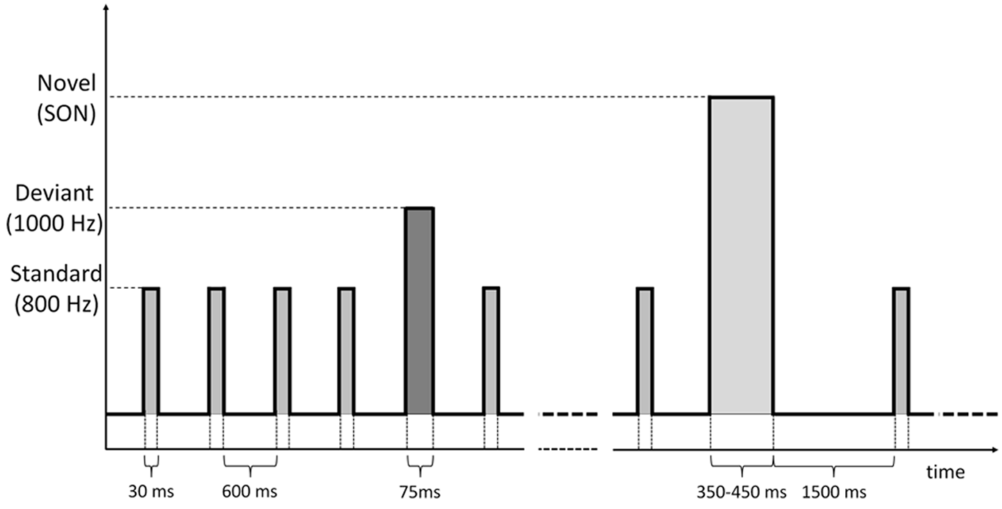

FIGURE 1 | Time sequence of standard, deviant and novel (SON) stimuli administered through the auditory oddball paradigm.

were averaged over epochs of 800 ms (including 200 ms before the stimulus onset). Responses to novel stimuli were averaged over 1700 ms duration epochs (including 200 ms before the stimulus onset). One VS patient (number 5 in **Table 1**) was excluded from the analysis because of the amount of artifacts due to teeth grinding (bruxism).

The ERP components identification was computed by means of a two-step process as reported in Fischer and coworkers (Guthrie and Buchwald, 1991; Fischer et al., 2008, 2010). The different ERP components were first qualitatively identified by means of the visual inspection by two neurophysiologists and successively validated by means of statistical analysis. The N100 evoked in response to standard and deviant tones was visually detected as a negative deflection (maximum peak amplitude >0.1 μV) occurring within 75–200 ms after stimulus onset. The MMN was identified as a negative deflection (maximum peak amplitude >0.75 μV) occurring within 200–350 ms after the stimulus occurrence. The novelty P300 (nP3) elicited in response to the subject's own name was visually detected as a positive deflection (maximum peak amplitude >0.75 μV) occurring between 250 and 1000 ms after the stimulus occurrence. The validation of ERP components (N100 and MMN) was performed comparing EEG epochs related to deviant and standard stimuli. Responses to deviant and novel stimuli were statistically compared to highlight the nP3 component. The waveforms were resampled by means of a bootstrap approach (Efron, 1979). The significance level of 5% was corrected by means of False Discovery Rate (FDR) to take into account multiple comparisons (Benjamini and Yekutieli, 2001). The FDR represents the expected proportion of erroneous rejections among all rejections. Considering V as the number of false positives (erroneous rejections) and S as the number of true positives (correct rejections), the FDR is given by:

$$FDR = E\left[\frac{V}{V+S}\right] \tag{1}$$

Let $H_1, H_2, \ldots, H_m$ be the null hypotheses, with m the number of univariate tests to be performed, and $p_1, p_2, \ldots, p_m$ their corresponding p-values. These values were ordered in increasing order ($p_1 \leq p_2 \leq \cdots \leq p_m$) and the value k was chosen as the largest i for which:

$$p_i \leq \frac{i}{m}\alpha \tag{2}$$

Therefore, the hypotheses $H(i)$ with $i = 1,\ldots, k$ must be rejected and thus p_i represents the new adjusted significance level.

Finally, a paired t-test between the resampled standard and deviant (or deviant and novel for nP3) distributions was performed for each sample within the selected time window. N100 and MMN waveforms were identified when 80% of samples within the time window showed a significant difference between standard and deviant stimuli. P300 waveforms were identified when at least 62 consecutive samples (60 ms) located around the maximum (positive) amplitude peak showed a significant difference between deviant and novel stimuli within the interval of 250–1000 ms (Fischer et al., 2008).

EEG activity recorded during baseline condition was subjected to a power spectral analysis. A Fast Fourier Transformation with a 1 s Hanning window was performed on EEG data to estimate the IAF parameter defined as the frequency associated to the highest power peak in alpha frequency range over the posterior electrodes (Klimesch, 1999).

STATISTICAL ANALYSIS

Mean latency and amplitude values of each ERP components (N100 passive condition, MMN passive condition, nP3 passive/active conditions) at the three midline electrodes (Fz, Cz, Pz) were calculated (according to the above describe procedures): data at Cz electrode position and the mean IAF peak values were considered for the between-group analysis. The group analysis comprised the VS ($n = 7$ patients) and MCS ($n = 7$ patients, including 3 patients initially diagnosed as MCS and 4 patients who evolved from VS to MCS) groups. The Mann-Whitney U-test and *Wilcoxon* signed-rank *test* were applied for the between-group (N100 passive condition, MMN passive condition, nP3 passive/active conditions, IAF peaks) and for the within-group analysis (nP3 passive/active condition), respectively.

The Spearman's rank correlation coefficient was calculated to estimate possible correlation between the nP3 mean amplitude and latency values (Cz) obtained for each condition (passive/active) and each recording session, and CRS-R total scores and auditory sub-scores obtained prior to each EEG recording. (FDR; Benjamini and Yekutieli, 2001) was applied to account for multiple correlations.

A significance threshold of 5% was set for all the statistical tests. All values are reported as mean ± Standard Deviation *(SD).*

RESULTS

N100 TO STANDARD TONES AND MMN TO DEVIANT TONES

Under passive condition, we found the N100 in all patients ($VS = -0.8 \pm 0.5\mu V$; MCS $= -0.75 \pm 0.7\mu V$) and it was significantly delayed in VS with respect to MCS group ($VS = 159.3 \pm 10.2$ ms; MCS $= 124.3 \pm 36.4$; Mann-Whitney U-test, $U_{(6)} = 35.5, p = 0.028$). Similarly, the MMN was observed in all patients, except patient 7 (**Table 1**) with no significant between group differences in latency ($VS = 339.2 \pm 155.6$ ms; MCS $= 268.3 \pm 22.6$ ms) and amplitude ($VS = -1.38 \pm 0.9\,\mu V$; MCS $= -1.27 \pm 0.4\,\mu V$) mean values.

NOVEL P300 TO SUBJECT OWN NAME

The novel P300 (nP3) was observed in all but one patient (patient 7, in **Table 2**). We found a significant delay in VS with respect to MCS group, ($VS = 515 \pm 210$ ms; MCS $= 407.5 \pm 65$ ms; Mann-Whitney U-test, $U_{(6)} = 26, p = 0.035$), only under passive listening condition (**Figure 2A**). Active listening condition elicited an nP3 with significantly larger amplitude (Mann-Whitney U-test, $U_{(6)} = 55, p = 0.009$) in MCS ($4.3 \pm 2.2\,\mu V$) as compared to VS group ($1.9 \pm 1\,\mu V$; **Figure 2B**). Finally, we noted the presence of a clear negative deflection, occurring at 80–100 ms from the nP3 that was interpreted as an instance of the N400.

When comparing passive vs. active conditions within the two groups, statistical analysis revealed that active condition was associated with a significantly larger nP3 mean amplitude in the

Table 2 | Average of the nP3 latency and amplitude values for each patient subject.

Patient	Diagnosis	nP3_passive condition		nP3_active condition	
		Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
1	MCS	345	2.2	375	3
2	VS	540	3	445	2.5
	MCS	345	3.7	300	3.4
3	VS	430	2.7	365	1.9
4	MCS	395	2.5	470	3.8
6	VS	430	2.4	415	1.1
7	VS	425	0.3	410	0.5
	MCS	455	0.9	330	0.3
8	VS	465	3.5	440	3.1
	MCS	455	5	440	6.6
9	VS	640	2	585	1.4
10	MCS	385	4.8	465	6.3
11	VS	585	1.8	585	1.8
	MCS	520	2	550	2.6

MCS patients (passive $= 3.4 \pm 1.5\,\mu$V; active $= 4.3 \pm 2.2\,\mu$V; Wilcoxon signed rank test, $W_{(6)} = 19$, $p = 0.0425$). On the contrary, the active condition elicited significantly smaller nP3 mean amplitude in the VS group (passive $= 2.6 \pm 1.1\,\mu$V; active $= 1.9 \pm 1\,\mu$V; Wilcoxon signed rank test, $W_{(6)} = 17$, $p = 0.0425$). No significant differences in the mean values of the nP3 latency detected in both conditions were found within patient groups.

Finally, a difference in the topography of the nP3 was observed between passive and active condition in MCS patients. As illustrated in **Figure 2** (panel B, insert on the right side) the nP3 shifted from frontal toward posterior scalp regions (mainly parietal) when changing from passive to active condition.

Four patients (patient number 2, 7, 8, 11 in **Table 1**) underwent a second recording session timely with the change of their clinical status from VS into MCS, according to the CRS-R score. We included patient 7 even if no detectable ERP late components (MMN, nP3) were evident in the first EEG recording. The N100 component was observed in all 4 patients with no significant differences in latency (156.2 ± 12.5 ms and 112.5 ± 43.7 ms, in the first and second recording session respectively) and amplitude (-0.8 ± 0.5 and $-0.9 \pm 0.8\,\mu$V, in the first and second recording session respectively). Similarly, we found the MMN component in all 4 patients (including the patient 7, with anoxic etiology) with no significant differences in latency (290 ± 52.9 and 262.5 ± 30.7 ms, in the first and second recording session respectively) and amplitude (-1.03 ± 0.2 and $-1.3 \pm 0.4\,\mu$V, in the first and second recording session, respectively).

In the second recording session as compared to the first one, we found a statistically significant increase in the nP3 amplitude, elicited by passive listening condition in patient 2 (nP3 amplitude of $3\,\mu$V and $3.7\,\mu$V, for the first and second recordings respectively; $p < 0.05$) and patient 8 (nP3 amplitude of $3.5\,\mu$V and $5\,\mu$V, for the first and second recordings, respectively; $p < 0.05$). Furthermore, the nP3 (passively) evoked during the second recording session displayed a change in the topography, being largely distributed over the frontal and posterior (parietal) scalp regions. In patient 11 and 8 no relevant changes were observed over time for both passive and active condition (**Figure 3**, P8 and P11).

POWER SPECTRA ANALYSIS

The mean IAF peak value estimated at Pz was 8.1 ± 0.89 Hz and 9.8 ± 1.57 Hz for the VS and MCS group, respectively. This IAF difference was statistically significant (*Wilcoxon* signed-rank *test*; $W_{(6)} = 17$, $p = 0.047$). It is worth to note that in patients 2, 8, and 11 an increase of the IAF peak occurred between the first and second recording ($P2 =$ from 7.5 to 10.5 Hz; $P8 = 10$ to 11.5 Hz; $P11 = 8.5$ to 9.5 Hz).

CLINICAL AND NEUROPHYSIOLOGICAL DATA CORRELATIONS

The CRS-R total scores obtained before each EEG recording and acquired from each patient were positively correlated with the amplitude of the nP3 elicited by the SON stimuli in the active condition ($r = 0.76$, $p = 0.004$; FDR correction; **Figure 4A**).

Furthermore, a positive correlation was found between the auditory sub-scale scores of the CRS-R and the amplitude of the nP3 recorded under the same experimental condition (i.e., active SON) ($r = 0.9$, $p = 0$; FDR correction; **Figure 4B**).

DISCUSSION

In this longitudinal pilot study, event related potential (ERP) components elicited by an auditory stimulation paradigm administered under passive (just listening) and active (counting subject's own names, SON) condition to a sample of patients diagnosed with disorder of consciousness (DOC) were investigated and ultimately correlated with the outcome of the clinical behavioral assessment followed-up during patients' rehabilitative period. Although we are aware of the limited power of the statistical findings due to the sample size, the main findings can be summarized as follows: (i) pre-attentive ERP components, such as N100, MMN and novelty P300 (nP3), were preserved in our sample of VS and MCS patients; (ii) when patients were asked to actively count novel stimuli (i.e., SON) the nP3 component displayed a significant increase in amplitude and a wider spatial distribution with respect to the passive listening only in MCS and not in VS patients, thus suggesting a preservation of less automatic attention ability in MCS; (iii) the same nP3 component elicited by passive listening of novel stimuli in some VS patients, could show a significant amplitude increment consistently with their moving from a VS to MCS; (iv) the occipito-parietal power alpha rhythm was higher in MCS with respect to VS; (v) finally, a positive correlation between amplitude of the nP3 elicited in the active condition and total score and auditory sub-scores of the CRS-R obtained from all patients corroborates the validity of such ERP

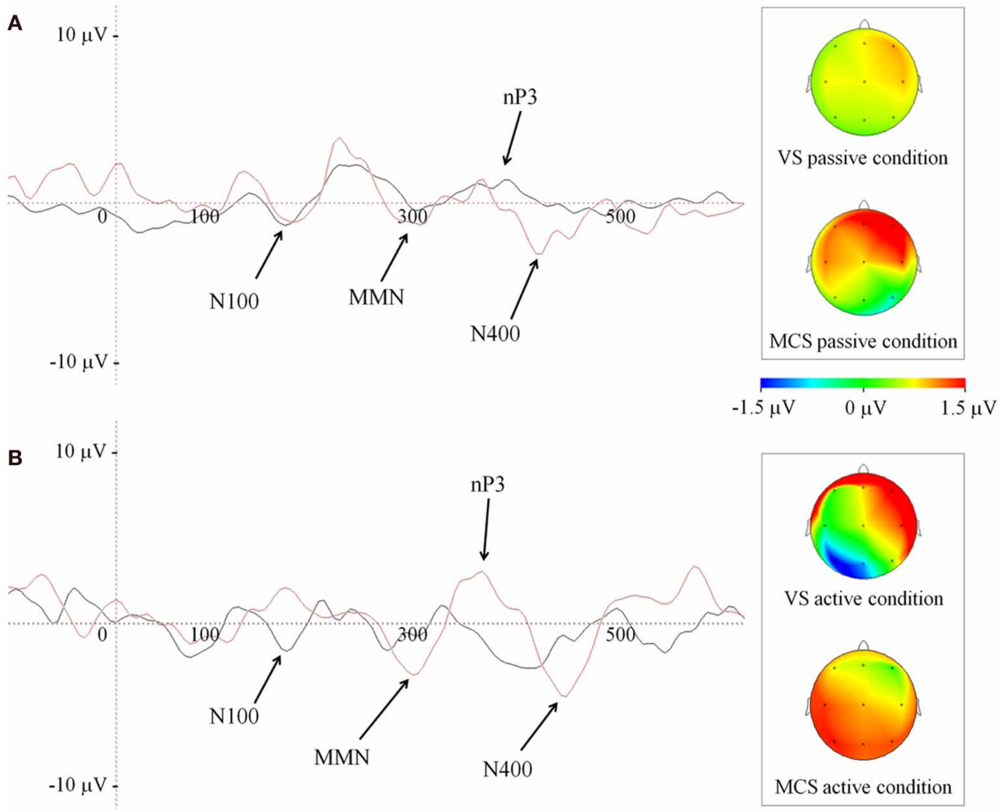

FIGURE 2 | Grand average of ERP waveforms depicted at Cz during passive (A) and active (B) listening of patients' own name (novel stimulus), in both group of patients. Black and red traces code for VS and MCS group, respectively. The right side panels illustrate the scalp nP3 topographies at Cz. Color bar code for the amplitudes of the scalp maps obtained at the time point of ERP maximum peak.

component in supporting the patient behavioral assessment that in turn, would improve the rehabilitation of such patients.

The presence of early ERP components, such as N100 indicates that the auditory sensorial register (Liegeois-Chauvel et al., 1994) was preserved in our sample of DOC patients. In line with previous evidence Glass et al., 1998; Guérit et al., 1999, the initial discrimination of the auditory target stimuli resulted to be delayed in our sample of VS as compared with MCS patients. It was suggested that prolongation of N100 latency might be related to a frontal lobe dysfunction (Jiang et al., 2000), with the prefrontal cortex being responsible for attentional resource modulation upon the sensory processing reflected by N100 (Coull, 1998). In our sample of patients, the DOC was the consequence of severe acquired brain injuries. The presence of brain lesions might have accounted for the N100 latency delay observed in VS patients, the majority of whom were at an earlier stage of the post-injury with respect to MCS.

The MMN component of ERPs did not show significant differences in mean latencies and amplitudes between the two groups of patients included in this study, thus suggesting that the automatic survey of the stimulus change (Näätänen, 1992; Näätänen et al., 2007) is rather preserved in VS and MCS patients. A similar lack of difference was reported in other studies dealing with VS and MCS patients with traumatic and non-traumatic etiology, in sub-acute and chronic stage (Kotchoubey et al., 2005; Fischer et al., 2010). The general conclusion was that such pre-attentive potential might not be selective to discriminate different DOCs. Our findings are in line with these conclusions. It is important to note that the one patient initially diagnosed as VS due to anoxia (Patient 7 in **Table 1**) showed a MMN component when she moved after 3 months to a MCS as indicated by the CRS-R scores. The occurrence of MMN has been reported as reliable predictor of recovery (Qin et al., 2008), particularly in the post-anoxic coma patients (Vanhaudenhuyse et al., 2008), although this etiology has been frequently reported as associated with a lack of evoked brain responses to auditory stimulation (Vanhaudenhuyse et al., 2008; Fischer et al., 2010).

The presence of a novelty P3 (nP3) elicited by SON paradigm has been already reported in patients with DOCs providing a useful tool to assess some residual cognitive functions in these behaviorally non- or minimally responsive conditions (Kotchoubey et al., 2004; Holeckova et al., 2006; Perrin et al., 2006; Fischer et al., 2008). Furthermore, in line with previous studies, (Kotchoubey et al., 2005; Perrin et al., 2006; Fischer et al., 2010), we found that all but one patient (Patient 7, **Table 1**) showed the nP3 component in response to a passive SON listening, regardless the clinical status (VS or MCS). As part of the P300 waveform complex, the nP3 is assumed to reflect aspects of the attentional orientation related to the working memory updating processes (Coles et al., 1988; Friedman et al., 2001), raising the

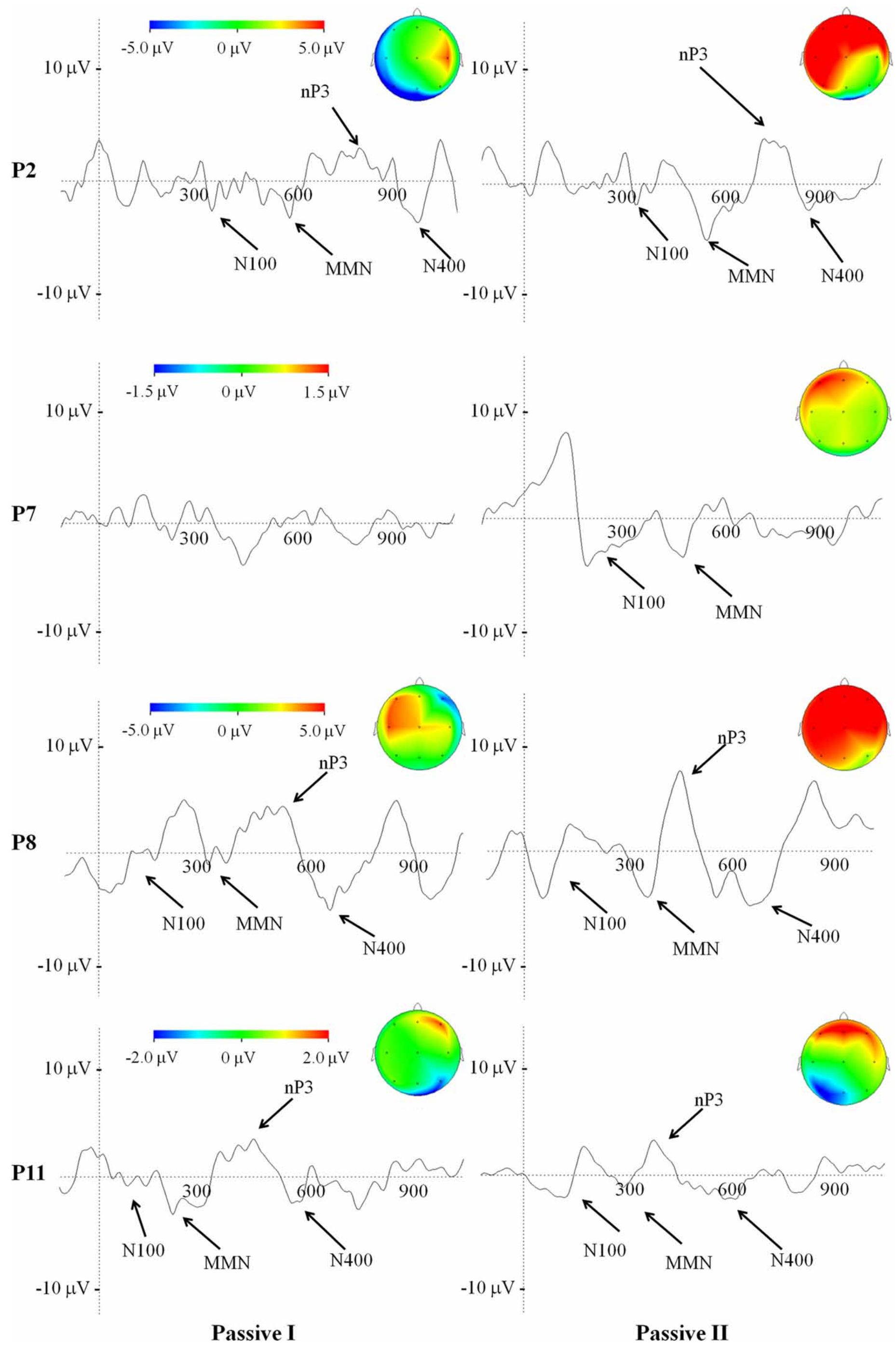

FIGURE 3 | Average of ERP waveforms and scalp potential topography depicted at Cz of passive condition related to the first and to the second recording session, in patients who underwent a change in their clinical status, according to the CRS-R. Color bar code for the amplitudes of the scalp maps and give the size of the nP3 projections at the time point of the maximum peak.

question of a residual maintenance of some higher-order cognitive processing in DOC patients, yet irrespective of the clinical diagnosis. The between group comparison revealed a significant delay of such component in the VS as compared to MCS sample of patients. The observed abnormality in the nP3 latency elicited in VS with respect to MCS might be indicative of a better ability to *unconsciously* detect novel events in MCS, although the different etiology, non-homogeneity of brain lesion extension and site in our patients could account for this abnormality as well.

Similar to already existing evidence (Schnakers et al., 2008, 2009b), the mean amplitude of the nP3 in response to SON was significantly larger in MCS patients when they were asked

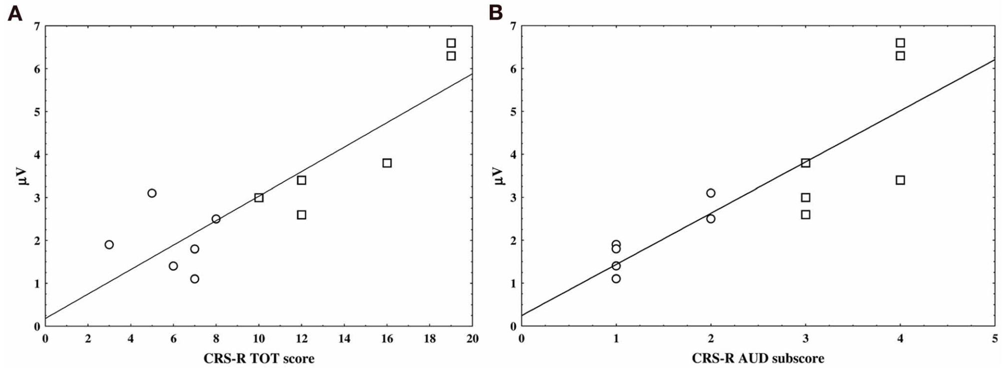

FIGURE 4 | The two scatter plots show the linear correlation between nP3 amplitude individual values in the active condition and the JFK CRS-R overall scores (panel A) and auditory sub-scores (panel B). VS and MCS patients are represented by circle and square, respectively.

to actively pay attention to the *novel* stimuli by counting his or her own name with respect to the solely listening to them. In the present study, we also investigated the topography of the nP3 elicited during active condition (vs. passive) and found a greater involvement of the posterior/parietal scalp areas in the MCS patients (**Figure 2**). Noticeably, a similar change in the nP3 topography elicited under passive condition occurred in 2 out of 4 patients (patient 2 and 8 in **Table 1**) who moved from VS to MCS (**Figure 3**). Our EEG topographical findings are concordant with previous studies that have shown the presence in MCS and VS of long-latency ERP components such as P300 family components which involve fronto-temporo-parietal cortices and backward connection between these areas, being these latter connectivity patterns considered as reliable markers for neuronal conscious perception (Del Cul et al., 2007; Garrido et al., 2007; Fischer et al., 2010; Boly et al., 2011). In this regard, it is worth to note that in our sample of MCS patients, an instance of N400 occurred in response to novel stimuli, particularly under active condition. This result can favor the idea of a preserved complex, albeit partially automatic (Perrin and Garcia-Larrea, 2003), of linguistic processing (Duncan et al., 2009) in such clinical status. Similarly, Perrin et al. (2006) reported that salient stimuli like SON could also elicit a N400 component in some DOC patients. The presence of this endogenous linguistic ERP, has been also associated with a good prognosis in consciousness disorders (Steppacher et al., 2013). Bearing in mind the caution when interpreting the presence of brain evoked responses in DOCs, the overall present findings on auditory nP3 generated under active condition, further extend previous reports in favor of a likely preserved ability in MCS patients to *consciously* orient their attention toward stimuli, following the instructions by the experimenter.

Specifically to the nature of the SON paradigm, it can be argued that the obtained responses to such stimuli are not name-specific. In fact, concomitant factors such as the lowest occurrence of the stimulus as novel, the longer stimulus duration, the complexity of its acoustic and semantic salience and the ecological salience to the subject, all contribute to the response elicited by SON. The difference in brain responses could be attributed to the meaning of the SON stimulus only if other factors were held constant, but this is not the case. The interaction of these four factors hinders the interpretation of the response to the SON and is the main limitation of the study. Anyway, even if one has to take into account the debatable name-specific nature of the SON stimulus responses, an active listening condition requiring the execution of a command (i.e., to count stimuli) still retains the value as a probe to test the patient's "following command ability" in absence of a recognizable motor output. These letters are instead, mandatory for the CRS-R clinical assessment based on execution upon verbal instructions of "simple" motor actions (like to turn the gaze, to take, to touch or to move something of his/her own body or in the environment).

On the contrary, with respect to what we have seen in MCS patients, we observed a significant decrease in the amplitude of the nP3 component evoked by SON under active as compared to passive condition, in our VS patients. We can only speculate that since the active was always preceded by the passive condition (to avoid patients to persevere in the task of counting) such opposite trend with respect to what observed in the MCS group, might be the result of fatigue and/or of limited attentional resources available in VS patients. In fact it cannot be ruled out that the overall length of the stimulation blocks (a relatively high number of trials were acquired in order to cope with the presence of artifacts) might have had a detrimental effect on the nP3 amplitude evoked in VS.

Finally, in a recent retrospective study on a cohort of 50 DOC patients, Babiloni and colleagues (Babiloni et al., 2009) have shown that the cortical alpha rhythms as measured also by means of the individual alpha peak (IAF; Klimesch, 1999) are altered in these patients according to their level of recovery from VS. In our small sample of patients, we only calculated the IAF (no source analysis was performed) and found that such EEG parameter was *normal* in both VS and MCS group of patients with a significant difference in favor of MCS (higher mean value). Even if no more advanced EEG processing is available in our study, we can consider this finding as a further surrogate of a preserved neurophysiological substrate of *conscious perception* in our sample of patients.

To our knowledge this is the first study which correlated the nP300 parameters with the CRS-R scores and reported a positive correlation between electrophysiological and clinical parameters as extracted from patients' evaluation over time. Accordingly, the amplitude of the nP3 components elicited by novel stimuli (SON) under active condition in our sample of DOC patients, positively correlated with the patient's CRS-R overall scores, being lower in VS and higher in MCS patients. As yet, such positive correlation was present between the auditory CRS-R sub-scores and the nP3 amplitude elicited in all patients during the active condition.

Although this latter finding might not be surprising since both behavioral and electrophysiological measures of the patient's ability to allocate attentional resources have exploited the auditory modality, it is of relevance that behavioral evolution of patients parallels changes in some ERP component as elicited during *voluntary* attention shifts. The correlation with the total scores of the clinical scale and the nP3 suggests that this ERP component is, however, affected by the overall level of brain functions assessed by means of the CRS-R and that thus its amplitude appears to be sensitive to the proportion of the overall improvement of single patient abilities.

The issue of correlations between clinical assessment based on behavioral tests and neuroimaging and electrophysiological data in DOC patients still remains a matter of debate. In fact, some studies did not find correlation between clinical and instrumental data (Di et al., 2007; Estraneo et al., 2013). On the other hand, more recent studies on DOC patients have found correlation between functional and structural brain connectivity patterns (at rest) and different levels of consciousness impairment as evaluated with CRS-R (Vanhaudenhuyse et al., 2010; Fernandez-Espejo et al., 2012). One plausible explanation for this still inconclusive results might be found in the non- homogeneity of patient cohorts in terms of DOC etiology (especially cerebral anoxia), time from event and site/side of brain lesions, among the different studies. Another source of discrepancy between correlation findings might be that correlations are reported with only CRS-R total scores and this has to be taken with caution as the diagnosis of DOC is based on the scores of the sub-scales and not on the overall score of the CRS-R.

Bearing in mind the limits of a pilot study, our overall findings confirm the added value of paraclinical testing based on EEG, as a means to disclose spared brain functions in DOC. Future investigations should address a follow-up longitudinal measurements in a large cohort of patients (especially the VS) to validate the predictive value of ERPs in following-up DOC evolution and to determine whether and to what extent clinical factors (i.e., the etiology, the site/size of brain lesions) can affect the several EEG parameter characteristics and their relevance in supporting the bedside management of such critical clinical conditions.

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Cyborg psychiatry to ensure agency and autonomy in mental disorders. A proposal for neuromodulation therapeutics

Jean-Arthur Micoulaud-Franchi[1,2]*, Guillaume Fond[3] and Guillaume Dumas[4,5]

[1] *Unité de Neurophysiologie, Psychophysiologie et Neurophénoménologie, Solaris, Pôle de Psychiatrie Universitaire, Hôpital Sainte-Marguerite, Marseille, France*
[2] *Laboratoire de Neurosciences Cognitives, UMR CNRS 7291, 31 Aix-Marseille Université, Site St Charles, Marseille, France*
[3] *Université Paris Est-Créteil, Pôle de Psychiatrie du Groupe des Hôpitaux Universitaires de Mondor, INSERM U955, Eq Psychiatrie Génétique, Fondation FondaMental Fondation de Coopération Scientifique en Santé Mentale, Paris, France*
[4] *Equipe Cogimage (ex-LENA CNRS UPR 640), CRICM - UPMC/INSERM UMR-S975/CNRS UMR7225, Paris, France*
[5] *Human Brain and Behavior Laboratory, Center for Complex Systems and Brain Sciences, Florida Atlantic University, Boca Raton, FL, USA*

Edited by:
Elisabeth V. C. Friedrich, University of Graz, Austria

Reviewed by:
Thorsten O. Zander, Max Planck Institute for Intelligent Systems, Germany
Klaus Mathiak, RWTH Aachen University, Germany

****Correspondence:***
Jean-Arthur Micoulaud-Franchi, Solaris, Pôle de Psychiatrie Universitaire, Hôpital Sainte-Marguerite, 270 Bd Sainte-Marguerite, 13009 Marseille, France
e-mail: jarthur.micoulaud@gmail.com

Neuromodulation therapeutics—as repeated Transcranial Magnetic Stimulation (rTMS) and neurofeedback—are valuable tools for psychiatry. Nevertheless, they currently face some limitations: rTMS has confounding effects on neural activation patterns, and neurofeedback fails to change neural dynamics in some cases. Here we propose how coupling rTMS and neurofeedback can tackle both issues by adapting neural activations during rTMS and actively guiding individuals during neurofeedback. An algorithmic challenge then consists in designing the proper recording, processing, feedback, and control of unwanted effects. But this new neuromodulation technique also poses an ethical challenge: ensuring treatment occurs within a biopsychosocial model of medicine, while considering both the interaction between the patients and the psychiatrist, and the maintenance of individuals' autonomy. Our solution is the concept of Cyborg psychiatry, which embodies the technique and includes a self-engaged interaction between patients and the neuromodulation device.

Keywords: brain computer interface, neurofeedback, non-invasive brain stimulation, transcranial magnetic stimulation, brain-state-dependent stimulation, mental disorder, psychiatry, neurocognitive networks

NON-INVASIVE ELECTROPHYSIOLOGICAL INTERVENTIONS IN PSYCHIATRY

A new therapeutic approach in psychiatry is to modulate neural networks of the brain in order to induce neural plasticity (Peled, 2005; Linden, 2006; Schneider et al., 2009; Thut and Pascual-Leone, 2010). However, traditional treatments for mental disorders such as pharmacology and psychotherapy give little consideration to the neural network dynamics (Mackey and Milton, 1987). Psychiatric drugs could have long-term neuroplastic effects but are difficult to adapt to each patient (Fond et al., 2012). Psychotherapies, in particular Cognitive Behavior Therapy (CBT), have an adaptive and interactive effect on the brain but it remains quite indirect (Goldapple et al., 2004). Two non-invasive electrophysiological interventions, however, are proving promising in brain therapeutics for mental disorders:

- Electrical brain stimulations devices: Transcranial Magnetic Stimulation (TMS; Miniussi and Rossini, 2011) and Transcranial Direct Current Stimulation (tDCS; Polania et al., 2010)
- Neurofeedback (NF) devices (Coben and Evans, 2011).

Repeated TMS (rTMS) and NF are valuable therapeutics in the field of psychiatry (Yucha and Montgomery, 2008; Coben and Evans, 2011), but with rTMS we are confronted with the confounding effects of brain-mind states and, with NF, difficulties to change neural dynamics could be a potential problem. In the current proposal our aim is twofold: (i) to explain how rTMS and NF coupling may offer a solution to the two aforementioned problems, and (ii) to analyze how these neuromodulation techniques may be integrated into an individual's brain dynamics and conception of him or herself as an autonomous agent (Glannon, 2013). In effect, we argue that the coupling of rTMS and NF can pave the way for a direct, adaptive, and interactive brain therapy in which patients can be self-engaged.

rTMS AND THE EFFECTS OF BRAIN-MIND STATES

Repetitive transcranial magnetic stimulation (rTMS) comprises a non-invasive and painless way to induce magnetic flux activation (high frequency) or inhibition (low frequency; Lisanby et al., 2002). Efficient in the treatment of psychiatric disorders, it has proved particularly robust for the treatment of major depressive episode (MDE), and results of its use in schizophrenia are encouraging (Lisanby et al., 2002; Coben and Evans, 2011). rTMS modifies neuronal activity in the selected superficial brain structure, but also modulates neural network activity (Lisanby et al., 2002; Huerta and Volpe, 2009). Thus, basic research carried out on TMS has led to the concept of "state dependency TMS" (Silvanto and Pascual-Leone, 2008). This concept suggests that the activation states of the neural circuits both before and during the stimulation influence the pulse effect. Indeed, TMS effect must be seen, not simply as the result of an applied stimulus, but as the result of the interaction between the applied stimulus and the level of brain activity (Silvanto and Pascual-Leone, 2008). Thus, the effects of rTMS are dependent on the brain-mind states of the stimulated subject (Bonnard et al., 2003). Therefore, current high variability of therapeutic effects of rTMS in mental disorders may be due in part to its partial account of individuals' neurodynamics and its effects on distant neural sites, even with localized stimulations (Vedeniapin et al., 2010).

Basic research suggests that rTMS efficiency could be increased in psychiatric disorders by triggering patients' brain activities during stimulation (Micoulaud-Franchi et al., 2013). Thus "interactive rTMS protocols" have been proposed (Micoulaud-Franchi et al., 2013). In NeuroAnalysis 2008 (Peled) said: "a future potential 'brain pacemaker' would probably involve a multiple-coil TMS device coupled with an EEG-dependent feedback mechanism, similar to a cardiac pacemaker set to act according to the ECG arrhythmias" (Peled, 2008). Thus, a "brain pacemaker," commonly referred to as "Brain-State-Dependent Stimulation" (BSDS; Walter et al., 2012), would comprise an adaptive TMS coupled to the ongoing brain activity; the stimulation would vary in time, intensity, frequency, and topography according to an on-line EEG feedback. EEG coupled TMS is "a technique that has come of age" (Fitzgerald, 2010) and offers new possibilities for the treatments of mental disorders (Thut and Pascual-Leone, 2010; Miniussi and Vallar, 2011). Price et al. show the first encouraging results of the use of this kind of adaptive/contingent rTMS in the treatment of MDE (Price et al., 2010).

NEUROFEEDBACK AND THE DIFFICULTIES TO CHANGE NEURAL DYNAMICS

NF is a non-invasive technique that enables an individual to learn the cognitive strategies required to change neurophysiological activity (i.e., EEG), for the purposes of improving health and performance (Yucha and Montgomery, 2008). The originality of NF is that it gives patients a more active role in there own health care (Yucha and Montgomery, 2008) and comprises a holistic conception in which cognitive and brain activities are modified together (Rémond, 1997; Cherici and Barbara, 2007; Coben and Evans, 2011). For this reason, NF is also referred to as "psychoneurotherapy" (Paquette et al., 2009), "brain psychotherapy" (Micoulaud-Franchi and Vion-Dury, 2011) or "neuroimagery therapy" (deCharms, 2008). Indeed, NF facilitates an on-line self-regulation of brain activity and as such may be considered as an adaptive and interactive brain therapy (Micoulaud-Franchi et al., 2012).

However, for certain subjects, modifying their neural dynamics through NF can prove very difficult. In a NF study aimed at investigating to what extent the regulation of excitability in cortical networks is impaired in epileptic patients, it was found that performance on NF was initially below healthy subjects and that "not every patient seemed to be able to achieve this control" (Rockstroh et al., 1993). This difficulty is also found in the field of Brain Computer Interface (BCI). BCI was developed, in particular, as assistive technology for patients with motor disabilities (Wang et al., 2010). BCI is commanded directly by brain activity feedback (EEG, MEG or fMRI activities measurements), with EEG activity constituting the most commonly used brain activity feedback. However, BCI performances show large variability across individuals, and for a non-negligible proportion of users (estimated at 15–30%), BCI control does not work (Vidaurre and Blankertz, 2010).

Many solutions have been proposed to optimize NF and BCI. Solutions based "on the participants" are closed to cognitive and behavioral therapeutics. The aims are to enhance the motivation of the participants, to help the participants to try different strategies, to explicit individual-specific control strategies and to apply the learned self-regulation skills in real-life situations (Kotchoubey et al., 2001). Solutions based "on the BCI loop," were proposed to optimize BCI performance. We suggest that some of these solutions could be applied to optimize NF for treatment of mental illness. The first involves an algorithmic solution that aims to develop a machine-learning mechanism (Vidaurre and Blankertz, 2010). It is in line with the concept of co-adaptation in which the tool becomes functionally involved in the extraction and definition of the user's goals: both subject and the tool are learning (Sanchez et al., 2009). The second solution comprises a "hybrid BCI," in which two BCIs are combined, for example: event-related (de)synchronization (ERD, ERS) of sensorimotor rhythms and steady-state visual evoked potentials (SSVEP; Pfurtscheller et al., 2010). The third solution comes from basic research in animals and invasive BCI. It uses closed-loop neural interface technology that combines neural ensemble decoding with simultaneous electrical microstimulation feedback (Marzullo et al., 2010; Mussa-Ivaldi et al., 2010). However, very few studies have used this solution to optimize BCI in humans (Walter et al., 2012). Birbaumer suggested: "The combination of these stimulation techniques (TMS, tDCS, neurochips) with BCIs is a largely unexplored field" (Birbaumer and Cohen, 2007), and, at the same time, research has yielded encouraging results showing that TMS may help participants to increase their brain EEG response performance in BCI (Kubler et al., 2002; Karim et al., 2004). This solution is, therefore, worthy of interest in the field of NF in psychiatry. Indeed, recurrent neuronal networks have been used to propose an interpretation of several mental dysfunctions (Pezard and Nandrino, 2001), which is evidence in itself that it is particularly difficult to modify one's brain activity when one has such mental disorders. Thus, rTMS could bring the necessary energy to break the recurrent neural network dynamics in order to help the patient explore new neural network dynamics and, by means of the NF device, change his/her EEG activity in the desired way to improve health and performance (Micoulaud-Franchi and Vion-Dury, 2011). tDCS may also enhance the effect of cognitive remediation techniques (Andrews et al., 2011) and could, thus, have the same positive effect on NF (Miniussi and Vallar, 2011).

COUPLING NON-INVASIVE ELECTROPHYSIOLOGICAL INTERVENTIONS

THE CHALLENGE OF CLOSING THE LOOP

To summarize, firstly TMS may be improved by taking into account brain activity (particularly EEG activity) to stimulate the brain (Price et al., 2010) and, secondly, NF could be improved by combining it with TMS or tDCS brain stimulation (Kubler et al., 2002). In addition, further research needs to be undertaken in this area to replicate the preliminary results in mental disorders (Price et al., 2010). However, here we propose to investigate the challenge of neuromodulation techniques that couple these two aforementioned improvements. We previously proposed the concept of "Neurofeedback rTMS" (Micoulaud-Franchi and Vion-Dury, 2011): in which the rTMS efficacy is enhanced by the background EEG, which is self-regulated by subjects through NF, and, at the same time, the subject is helped by the rTMS to create this background EEG. TMS/tDCS-NF coupling can, therefore, close the loop completely in order to optimize simultaneously the non-invasive neurostimulation techniques and the NF, See **Figure 1**. TMS/tDCS-NF coupling is, however, confronted by two challenges: the first is algorithmic, the second is ethic.

The algorithmic challenge involves determining the kind of brain activity that will be recorded and the kind of feedback that will be made, how all these data will be treated in real time and how to control unwanted effects. The first issue is related to the use of a new diagnostic system correlated to the neural network disturbance in mental disorders. The "Clinical Brain Profiling" advanced by Peled is an interesting approach to these novel therapeutic hypotheses based on TMS/tDCS-NF coupling (Peled, 2006, 2009). Peled proposed a new etiology-oriented diagnostic system for psychiatry based on neural network dynamics complexity and neural plasticity (Peled, 2004). It provides an innovative heuristic for recording brain activity and will soon integrate data from TMS-EEG research (Ilmoniemi et al., 1997; Thut and Pascual-Leone, 2010). The second issue related to such approaches is how to better account for non-linear dynamics in neuroscience. This is already being tackled at the theoretical levels, but relies, also, on the development of new methods. One such novel method is the "dynamic clamp" advanced by Prinz et al. (2004), which consists in dynamically interfacing living cells with their simulated counterpart. This technique creates a "hybrid network" incorporating the inherent nonlinearities of most physiological processes (Prinz et al., 2004). Such a concept has been already scaled from the neural to the behavioral scale with the so-called "Virtual Partner Interaction" (VPI; Kelso et al., 2009). VPI could constitute a paradigmatic model for the therapeutic approach described in the current paper (Werry et al., 2001). The last algorithmic issue is related to some problems appearing in closed loop systems (Corke and Good, 1996). Indeed, a closed loop feedback system based on NF and rTMS/tDCS could lead to unforeseeable "resonance" effects in the brain that should be investigated and be taken into account.

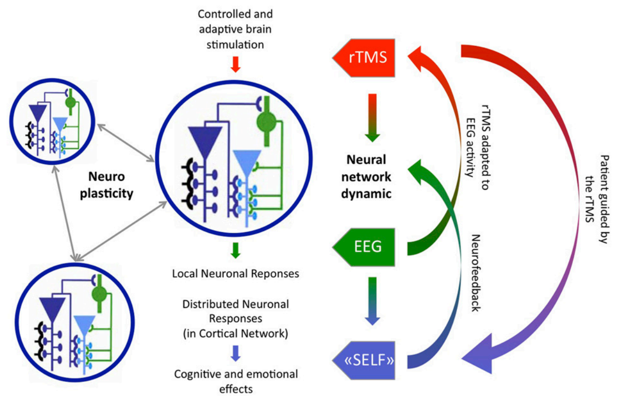

FIGURE 1 | Combination of Brain-State-Dependent Stimulation (green-red loop) and Neurofeedback rTMS (blue-red loop) as an example of Cyborg psychiatry device, adapted from Thut and Pascual-Leone (2010).

The ethic challenge is in line with the general aim of psychiatry, which tries to enable patients to lead a more self-determined life. Indeed, psychiatry increasingly uses neuromodulation techniques in the treatment of mental disorders. For example, the Mind Machine Project (MMP) initiated in 2009 by the Massachusetts Institute of Technology (MIT) is "looking for advanced applications of these technologies, such as "non-chemical based" solutions for psychiatric treatments and brain prostheses." In addition the concept of neurorehabilitation has been applied in the field of psychiatry (Bach-Y-Rita, 2003; Miniussi and Rossini, 2011; Miniussi and Vallar, 2011). Thus, the question is: how can we ensure that all these techniques restore or enhance a person's agency and autonomy? Related to this, we propose a first ethical issue based on the biopsychosocial model of medicine and a third person perspective (Glannon, 2013). This issue is related to the fact that these neuromodulation techniques depend on the interaction between the learner (subjects) and the trainer (practitioner/therapist), and are constructed as a process that occurs within a biopsychosocial context and social constraints (Glannon, 2013). We also put forward a second, more radical, ethical issue based on a neurophenomenological point of view and a first person perspective. Here we suggest that agency and autonomy depend on the capacity of all these techniques to be embodied by the patients. Such an approach is already present in closed loop technology for sensory substitution (Bach-Y-Rita, 2003; Bach-Y-Rita and Kercel, 2003). The ethical issue is ensured by the fact that the subject used the device as a part of his/her body. The device has to open up a world to the subject that will be appropriated by himself or herself. Similarly, TMS/tDCS-NF coupling could help patients to promote therapeutic neural plasticity using their own brain connectivity and without the direct intervention a third party (Linden, 2006; Schneider et al., 2009). Of course, psychiatrists should still help the patients, but the important point is that the device enables the subject to rediscover their own mind-brain world and from their own first person perspective. This ethical point of view leads us to the concept of Cyborg.

BACK TO THE CYBORG CONCEPT AS AN HEURISTIC FOR CUTTING ACROSS MIND, BRAIN AND DEVICES

"Cyborg" is a term coined in 1960s, in the context of the challenges presented by space flight and travel, with the famous article entitled "Cyborgs and Space," by Kline, a psychiatrist at Rockland State Hospital, and Clynes, a scientist at the Dynamic Simulation Lab (Clynes and Kline, 1960; Gray, 1995). "Cyborg" combined the words "cybernetic" and "organism." The concept involves devices that enable an organism to live outside its habitat (in this case: Space): "The Cyborg deliberately incorporates exogenous components extending the self-regulatory control function of the organism in order to adapt it to new environments" (Clynes and Kline, 1960). Consequently, a Cyborg is a kind of extended embodiment, an organism that is, at the same time, natural and artificial, and, as such, questions the limits between organism, technology and external environment (Tomas, 1995).

In 1970, Clynes wrote, this time without Kline, a second Cyborg article entitled "Sentic space travel" (Clynes, 1995). This Sentic Cyborg involves devices that enable a human "to express his emotion in accordance with his nature" to enable them to carry out very long space-flights (Gray, 1995). Initially refused, Clynes' proposition is now of theoretical interest in light of the new possibilities of cognitivo-brain modulation using TMS/tDCS and NF. Kline and Clynes' original question, "What are some of the devices necessary for creating self-regulating man-machine systems (…) to unconsciously adapt it to new environments?" (Clynes and Kline, 1960), can now be rephrased as: What are the devices needed to create self-regulating brain-machine systems to be used by patients with mental disorders to promote new brain/mind dynamics? By extending the first Cyborg hypothesis of Kline and Clynes, the new direct, adaptive, and interactive brain therapies proposed in this paper could not only open the door to new ways of interacting with the outside (Space), but also create new possibilities of dealing with the inside (brain-mind).

As Clynes suggested in the conclusion of his Sentic Cyborg hypothesis: "Through understanding our unconscious heritage consciously, we may be able to teach our automatic systems to live in harmony with our old heritage, as well as with our new exploration of outer, and perforce, inner, space" (Clynes, 1995). The benefit of the cyborg hypothesis is that it leads the psychiatrist to consider neurostimulation techniques (as TMS or tDCS), not just as an outside brain constraint, but also as a brain guidance interaction in which the patient's mind is self-engaged. This hypothetical point of view is meanly theoretical and need to be tested with some experimental observations in order to confirm its effectiveness and its lack of unwanted and side effects as "resonant" effects (Corke and Good, 1996). However, we wanted to stress that the future of neuromodulation treatments for mental disorders will involve dealing, firstly, with neural network dynamics (Peled, 2006, 2008) and, secondly, with the capacity of the treatment to exploit the point of view of the patients, to act as a cyborg device.

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