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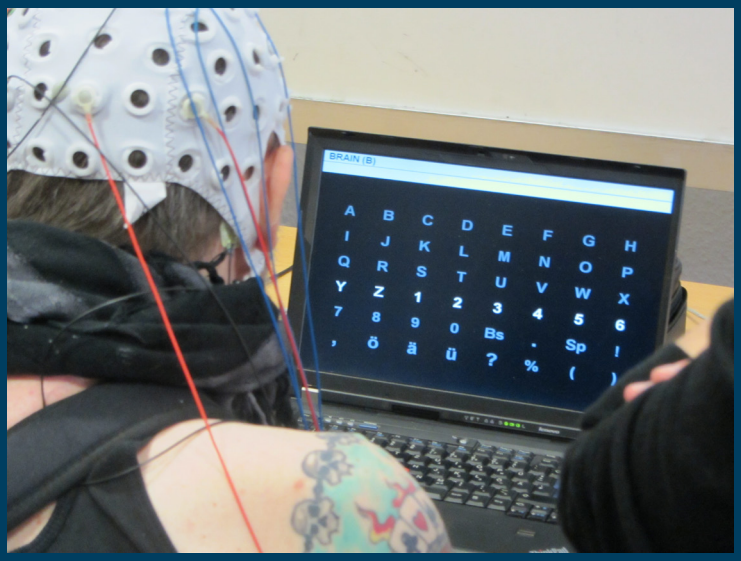

INTERACTION OF BCI WITH THE UNDERLYING NEUROLOGICAL CONDITIONS IN PATIENTS: PROS AND CONS

Topic Editors
Aleksandra Vuckovic, Jaime A. Pineda, Kristen LaMarca, Disha Gupta and Christoph Guger

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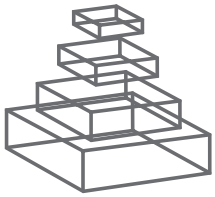

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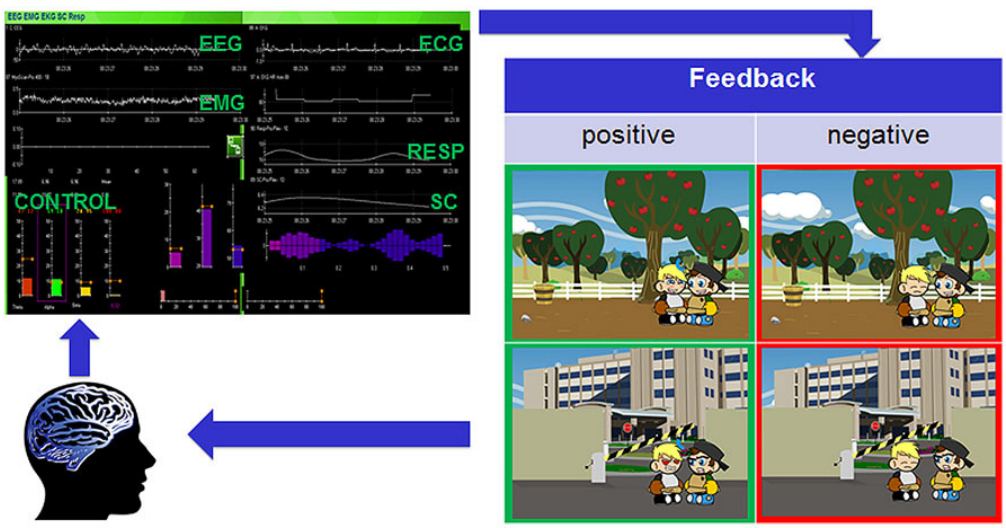

The subject's EEG is recorded using BioInfiniti, a Thought Technology Ltd. software that measures EEG, EMG, ECG, respiration and skin conductance. The EEG signal is fed into the game itself and provides the user with visual feedback (positive feedback indicated in green and negative feedback in red). Through this feedback, subjects learn to change brain activity voluntarily and thus control the game. In the social interaction sequences, the child's avatar (i.e. child with the blond hair) must approach the non-player character (NPC; child with the hat) and while facing him, the player has to

change mu power volitionally. In the course of sessions, mu is shaped to increase and theta and beta frequencies were shaped to decrease. The rewarding feedback is the child's avatar imitating the facial emotion of the NPC. Figure taken from Friedrich EVC, Suttie N, Sivanathan A, Lim T, Louchart S and Pineda JA (2014) Brain–computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum. Front. Neuroeng. 7:21. doi: 10.3389/fneng.2014.00021.

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EDITORIAL
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Interaction of BCI with the underlying neurological conditions in patients: pros and cons

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Keywords: BCI performance, patients, amyothopic lateral sclerosys, spinal cord injury, autism spectrum disorders, stroke volume, cerebral palsy

The primary purpose of clinical Brain Computer Interface (BCI) systems is to help patients communicate with their environment or to aid in their recovery. BCI can be used to replace, restore, enhance, supplement, or improve natural Central Neural System (CNS) output (Wolpaw and Wolpaw, 2012).

A common denominator for all BCI patient groups is that they suffer from a neurological deficit. As a consequence, BCI systems in clinical and research settings operate with control signals (brain waves) that could be substantially altered compared to brain waves of able-bodied individuals. Most BCI systems are built and tested on able-bodied individuals, being insufficiently robust for clinical applications. The main reason for this is a lack of systematic analysis on how different neurological problems affect the BCI performance.

This special issue highlights interaction of BCI systems with the underlying neurological problems and how performance of these BCI system differ compared to similar systems tested on healthy individuals. The issue presents 4 reviews (Friedrich et al., 2014; Pineda et al., 2014; Priftis, 2014; Rupp, 2014) and 8 experimental studies (Ang et al., 2014; Daly et al., 2014; Ono et al., 2014; Song et al., 2014; Xu et al., 2014; Young et al., 2014a,b,c). It covers studies on five different patient groups: stroke (Ang et al., 2014; Ono et al., 2014; Song et al., 2014; Young et al., 2014a,b,c), spinal cord injury (SCI) (Rupp, 2014; Xu et al., 2014), autism (Friedrich et al., 2014; Pineda et al., 2014), cerebral palsy (CP) (Daly et al., 2014) and amyotrophic lateral sclerosis (ALS) (Priftis, 2014). Three different types of BCI are presented: motor imagery, P300 and neurofeedback (operant conditioning). In the presented papers, BCI has been used either on its own or in a combination with an external device such as a robot or a functional electrical stimulation (FES).

Review papers discuss several possible applications of BCI including methods to replace (Priftis, 2014; Rupp, 2014), restore (Rupp, 2014) and improve (Friedrich et al., 2014; Pineda et al., 2014; Rupp, 2014) natural CNP output. Several experimental studies in this special issue present BCI applications to improve and restore CNP functions (Ang et al., 2014; Ono et al., 2014; Young et al., 2014a,b) while some present basic research papers looking into the effect of BCI training on the cortical activity (Song et al., 2014; Young et al., 2014b,c) or exploring EEG signature characteristic for a certain patient group, such as SCI or CP (Daly et al., 2014; Xu et al., 2014).

In two review articles Pineda et al. and Friedrich et al. look into the application of BCI on a relatively novel group of patients, autistic children, who show deficits in social and communicative skills, including imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors. They discuss evidences for model-based neurofeedback approach for treating autism and propose a BCI game for treating both high and low functioning autistic patients. The game is unique in that it includes social interactions and provides neural- and body-based feedback that corresponds directly to the underlying significance of the trained signals as well as to the behavior that is reinforced. A review by Rupp provides a comprehensive critical analysis of pros- and cons- of different types of BCI for spinal cord injured patients. He also discusses advantages and disadvantages of using BCI for communication, wheelchair and environmental control, control of neuroprosthesis and for clinical, rehabilitation purposes. This paper provides a valuable analysis of different medical and personal factors which might affect the performance of a BCI. While some of these factors are specific for spinal cord injured patients, many of them would exist in most patient groups using BCI. A review paper by Priftis provides a critical analysis of the evidences of the effectiveness of P300 speller as a communication tool for ALS patients. This is one of the rare application for which a commercially available solution exists (intendix, g.tec medical engineering GmbH, g.USBamp P300 model, Guger Technologies OG, Austria). While accuracy of this type of BCI reaches 90% in able-bodied, only 70% can be achieved in patients (Ortner et al., 2011). Priftis (2014) therefore concluded that requirements of ALS patients haven't been met yet, and highlights a striking fact that a tiny portion of published papers on P300 BCI presents experimental studies on ALS patients.

Papers showing experimental results in the special issue are either oriented toward rehabilitation or toward a basic science research. Stroke remains the most frequently tested patient population. In a randomized controlled trial on 21 chronic stroke patients, Ang et al. compare three hand and arm rehabilitation therapies, BCI with a haptic knob (HK) robot, HK alone or a

standard physiotherapy. They provided evidences for BCI-HK group achieving significantly larger motor gain than the other two groups.

Ono et al. combined motor imagery based BCI with two different types of feedback for rehabilitation of hand function in chronic stroke patients; a visual and somatosensory. While both feedback modalities increased cortical response, as measured by the intensity of event-related desynchronization (ERD), only BCI training with somatosensory feedback provided improved motor function. This paper therefore demonstrates that changes in the cortical level might not necessarily be indicators of functional recovery.

An interesting case study by Young et al. (2014a), which fits well with the topic of the special issue, investigated how the pre-existing neurological condition (congenital deafness) of a stroke patient influences performance of BCI system used for motor rehabilitation. The same research group provided a comprehensive analysis on the influence of BCI training on functional brain connectivity and brain organization, as measured by EEG and fMRI and it's relation to motor gains (Song et al., 2014; Young et al., 2014b,c). In a controlled study on 14 chronic hemiplegic patients they showed that only a treatment group, which received BCI-FES therapy, showed differential changes in brain activity patterns between lesioned and non lesioned hemisphere, which were associated with changes in a specific motor function (Young et al., 2014b). Using diffusion tensor imagining they showed that baseline fractional anisotropy of the posterior limb of the internal capsule predicts motor recovery (Song et al., 2014). They also used fMRI to measure brain activity in stroke patients in a simple tapping task before and after a BCI intervention, showing that task-based functional connectivity correlates with gain in the motor outcome. However they also gave a word of warning indicating that BCI therapy might produce both adaptive and maladaptive changes (Young et al., 2014c).

Xu et al. compared movement related cortical potentials (MRCP) between three groups: able bodied volunteers, chronic paraplegic patients with central neuropathic pain and chronic paraplegic patients with no pain. They found significantly larger MRCP in both paraplegic patients groups compared to able-bodied people, independent on the underlying sensory loss or presence of chronic pain. This contrasts studies based on ERD analysis, in which paralysis and pain showed differential effect on the activity of the sensory-motor cortex (Vuckovic et al., 2014) and in which paraplegic patients with no pain have weaker ERD signatures than able-bodied people (Pfurtscheller et al., 2009; Vuckovic et al., 2014); the study indicates that in this patient group, for motor imagery based BCI, time and phase locked MRCP might be a better suited feature than time but not phase locked ERD.

Daly et al. provided one of the rare BCI studies on adults with CP. They showed that motor imagery in patients with CP results in significantly less ERD and less functional connectivity compared to the able-bodied, indicating potentially lower BCI performances.

In summary, for BCIs it is still a long way to presenting an adequate replacement of the existing technologies for communication and control in patients with a minimum of preserved motor and cognitive function. Rehabilitation seems to be the area which provides the most immediate measure of benefit to a user. Rehabilitation is limited to a certain period of time and is typically performed in clinical environment, therefore can be operated by a clinically trained person. Recent tendencies to prolonged, home based rehabilitation will however likely increase requirements for a rehabilitation BCI in respect to size, price, esthetic, and user friendliness.

We are optimistic that this special issue will generate a body of knowledge valuable both to researchers working with clinical populations, but also to a vast majority of BCI researchers testing new algorithms on able-bodied people. This should lead toward more robust or tailor-made BCI protocols, facilitating translation of research from laboratories to the end users.

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PERSPECTIVE ARTICLE
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Neurorehabilitation of social dysfunctions: a model-based neurofeedback approach for low and high-functioning autism

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Autism Spectrum Disorder (ASD) is an increasingly prevalent condition with core deficits in the social domain. Understanding its neuroetiology is critical to providing insights into the relationship between neuroanatomy, physiology and social behaviors, including imitation learning, language, empathy, theory of mind, and even self-awareness. Equally important is the need to find ways to arrest its increasing prevalence and to ameliorate its symptoms. In this review, we highlight neurofeedback studies as viable treatment options for high-functioning as well as low-functioning children with ASD. Lower-functioning groups have the greatest need for diagnosis and treatment, the greatest barrier to communication, and may experience the greatest benefit if a treatment can improve function or prevent progression of the disorder at an early stage. Therefore, we focus on neurofeedback interventions combined with other kinds of behavioral conditioning to induce neuroplastic changes that can address the full spectrum of the autism phenotype.

Keywords: neurofeedback training, autism, low functioning autism, autism spectrum disorders, intervention studies, classical conditioning

AIM

In this review, we highlight preliminary yet promising observations to support the hypothesis that neurofeedback training (NFT) in combination with a new behavioral intervention, TAGteach, is a viable treatment option not only for high-functioning but also for low-functioning children with ASD.

SYMPTOMS

Autism Spectrum Disorder (ASD) is now estimated to affect 1 in 68 children (Baio, 2014), who show marked deficits in social and communicative skills, including imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors. These problems significantly affect social interactions and prevent children from establishing normal social relationships with others. The ASD phenotype varies in severity and character, encompassing individuals who are asocial but otherwise high-functioning (sometimes at the "savant" level), and low-functioning non-verbal individuals. The distinction between low and high-functioning autism is typically based on the child's IQ, with the cutoff being around 80. At the high-functioning end of the spectrum, the deficits primarily impair social interactions and prevent children from establishing adequate relations with others. At the low-functioning end, children show interactions mainly with the goal of behavior regulation such as protesting rather than social engagement (Maljaars et al., 2012).

CAUSES AND BRAIN CORRELATES

Different models to explain autism have been proposed, but the neuroetiology of autism is not yet entirely understood. Rubenstein and Merzenich (2003) have proposed an "increased ratio of excitation/inhibition in sensory, mnemonic, social and emotional systems", which can be caused by a combination of environmental and genetic factors. Another working hypothesis is that a dysfunction in motor processing, specifically in the mirror neuron system (MNS; di Pellegrino et al., 1992; Williams et al., 2001; Rizzolatti and Craighero, 2004), is an underlying factor in the condition. In one anatomical MRI study, Hadjikhani et al. (2006) examined 14 high-functioning adults with ASD and observed significant cortical thinning compared to matched control participants. These differences were found in areas considered part of the classic MNS, such as the inferior frontal gyrus (IFG), bilateral inferior parietal lobule (IPL), as well as right superior temporal sulcus (STS). These findings have been strengthened by significant correlations with autism symptoms, as diagnosed by the autism diagnostic interview-revised or ADI-R (Lord et al., 1994). Williams et al. (2006) studied 16 adolescents with ASD during finger movement imitation. Although no effects were detected in IFG, a comparison with matched typically developing (TD) children showed reduced activation for the ASD group in bilateral IPL. Dapretto et al. (2006) reported reduced activation in IFG in another fMRI study in which they tested nine boys with ASD during imitation of emotional facial expressions. Although children were able to perform the imitation task, significantly reduced activation in IFG was detected bilaterally in a comparison with controls. In contrast, Martineau et al. (2010) reported hyperactivation of the pars opercularis (belonging to the MNS) during observation of human motion in autistic subjects compared to controls. Baastiaansen et al.

(2011) reported that IFG activity during the observation of facial expressions increased with age in subjects with autism, but not in controls, suggesting improved social functioning with age. In terms of functional connectivity, Villalobos et al. (2005) found reduced fMRI connectivity between primary visual cortex and bilateral IFG during visuomotor coordination in eight participants with ASD, compared to matched TD participants. Likewise, studies using resting state (rs)-magnetoencephalography (MEG) or quantitative electroencephalography (QEEG) support the notion of dysfunctional connectivity in ASD. Tsiaras et al. (2011) showed reduced interdependence strength within bilateral frontal and temporal sensors, as well as between temporal sensors and other recording sites in a group of ASD participants. Cornew et al. (2012) indicated that children with ASD exhibited regionally specific elevations in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and high frequency (20–120 Hz) power, supporting an imbalance of neural excitation/inhibition as a neurobiological feature of ASD. Billeci et al. (2013) showed that children with ASD present several differences in power spectra, coherence, and symmetry measures compared to controls. This is true both when the signals are acquired in resting conditions—with either open or closed eyes—and when specific tasks are performed. For all these reasons it is speculated that abnormal functional connections exist that can lead to ineffective or atypical neural communication, which in turn may impede early affective, social and communicative development. This suggests that a reasonable therapeutic approach for the treatment of ASD is to normalize abnormal functional connections (Pineda et al., 2012). However, most of these findings rely on data from high-functioning individuals (Dapretto et al., 2006). As IQ correlates with brain volume (Posthuma et al., 2002; Posthuma and Polderman, 2013), brain structure (Price et al., 2013) and brain function (van den Bos et al., 2012), it has yet to be shown if a generalization of these results to the lower end of the spectrum is justified.

TREATMENTS

In clinical studies, the most effective type of therapy for ASD has been behavioral intervention, with an efficacy rate of approximately 48% (Lovaas, 1987; McEachin et al., 1993; Smith et al., 2009). However, behavioral therapy is time consuming and costly for such a low potential benefit, making it entirely out of reach to the majority of the affected population, especially in developing countries. Moreover, research aimed at interventions is predominantly conducted with high-functioning adults or adolescents and a review of the literature confirms that social skills training for ASD mostly involves high-functioning children (Cappadocia et al., 2012; Wainer and Ingersoll, 2013). However, it is the younger lower-functioning groups that have the greatest need for diagnosis and treatment, who have the greatest barrier to communication (and hence the greatest need for replacement or enhancement of communication), and who may experience the greatest benefit if such tools can improve function or prevent progression of the disorder at an early stage. Ben et al. (2008, 2011) reported better outcome in behavioral therapy for children with an IQ above 70 and less severe symptoms than for children with an IQ below 70 and more deficits. This emphasizes that different treatment approaches are needed and should be used for lower functioning children on the spectrum. Thus, alternative interventions that normalize social behavior would be beneficial and warrant serious consideration.

One alternative to behavioral therapy is NFT. NFT allows for visualization of brain activity to be fed back to a user by means of a computer in a closed "neurofeedback" loop, allowing subjects to learn to control the natural operation of brain rhythms *in vivo* and in near real time (Nowlis and Kamiya, 1970; Delorme and Makeig, 2004; Delorme et al., 2011). Brain electrical rhythms are instantiated across different spatial scales (Buzsáki and Draguhn, 2004) from single neurons (Hutcheon and Yarom, 2000), to neuronal circuits (Whittington et al., 1997), to re-entrant thalamocortical and large-scale cortico-cortical networks (Lorincz et al., 2009). It is assumed that these rhythms enable the dynamic routing and gating of information via the synchronization of various bits of information (Salinas and Sejnowski, 2001; Schoffelen et al., 2005; Jensen and Mazaheri, 2010). From a systems level perspective, electroencephalographic (EEG) responses to sensory stimuli can partially be explained by transient, stimulus-induced adjustment in the phase of ongoing rhythms via phase-resetting (Sayers et al., 1974; Makeig et al., 2002; Klimesch et al., 2007). The possibility of self-directed modulation of these rhythms and phase adjustments raises an interesting set of questions. Is it possible to promote/enhance or inhibit/suppress rhythmic oscillations in distinct neural networks *in vivo*? Can we modulate these rhythms volitionally through some periodic internal input or drive? Theoretically, a functional impact is possible through the modulation of brain rhythms that may play a causal role in specific cognitive functioning.

There is consensus that EEG activity recorded on the scalp arises mainly from cortex (Pantev et al., 1991; Llinás and Ribary, 1993). Neurons firing in synchrony while an individual is at rest produce large amplitude oscillations detected over various brain regions (Hari et al., 1997; Klimesch, 1997; Pfurtscheller et al., 1997, 2000; Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004). The mu rhythm is such an oscillation in the 8–13 Hz band, limited to brief periods of 0.5–2 s duration and recorded in the absence of movement over sensorimotor cortex. Activation by self-movement, the observation of movement, and even the imagination of movement produces desynchronization and a suppression of mu rhythm activity (Salmelin and Hari, 1994; Pfurtscheller et al., 1997). The link between mu rhythms and mirroring activity was first proposed by Altschuler et al. (1998), and thereafter by other researchers (Cochin et al., 1998, 1999; Hari et al., 2000). More recent studies have found that mu rhythm is modulated by object-directed actions (Muthukumaraswamy and Johnson, 2004). Since it is generated by activity in sensorimotor areas and mirror neurons have been located primarily in premotor areas, it is hypothesized that mu rhythm indexes downstream modulation of primary sensorimotor areas by mirroring activity in frontal cortex (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004; Oberman et al., 2005; Pineda, 2005). Furthermore, TD individuals can learn to modulate mu rhythms via NFT (Pineda et al., 2000, 2003), and while normal individuals exhibit

mu suppression to both self-directed and observed movement, high-functioning ASD individuals fail to exhibit mu suppression to observed movement (Oberman et al., 2005).

Most NFT approaches use a simple visual stimulus or game to train individuals to increase/decrease a particular bandwidth of the EEG signal. With training, the majority of individuals develop a high level of conscious and unconscious control over their brain activity. During training, subjects are exposed to the same visual/auditory feedback or reward stimuli, and hence the entrained EEG differences most likely represent the modulation of some internal brain state associated with the event rather than to external factors. While the precise mechanisms of how using neurofeedback can induce changes in the brain are unclear, the evidence suggests they capitalize on the innate plasticity of the brain to produce neural, functional, and ultimately behavioral changes. Furthermore, the use of QEEG (Cantor and Chabot, 2009; Coben and Myers, 2010; Thompson et al., 2010a,b) combined with specific and individualized protocols (e.g., amplitude and coherence training) can help fit the training to the heterogeneity of autistic symptomatology.

The majority of studies using neurofeedback for ASD includes children at the higher end of the autism spectrum and these studies have reported significant normalization of brain functioning as well as improvement in behavior and cognitive function (Pineda et al., 2008; Kouijzer et al., 2009; Coben et al., 2010). However, the generalization of these findings to adults or very young and lower functioning children is not yet well examined (Coben et al., 2010). One concern is whether nonverbal children even understand instructions and can process the meaning of feedback. High functioning individuals seem to process external, concrete feedback in a way similar to their TD peers (Larson et al., 2012). However, a recent study suggested that nonverbal low functioning individuals with ASD are able to attribute goals to other persons but are not able to consider the person's circumstances or the context to interpret the actions and attribute intentions as most typical developing children do (Somogyi et al., 2013). Indeed, neurofeedback-based learning is correlated with IQ (van den Bos et al., 2012).

TREATMENT FOR LOW-FUNCTIONING CHILDREN WITH AUTISM: TEACHING WITH ACOUSTICAL GUIDANCE AND NFT

Operant and classical conditioning principles have been key to the behavioral treatment of autism for decades (Helm, 1976; Neuringer, 2002; Pickett et al., 2009). Secondary or conditioned reinforcers, such as auditory markers, have been shown to enhance learning, including the learning of complex sequences of behaviors, through the value acquired from their associations with primary reinforcers. As lower functioning children with ASD have a greater degree of social, language, and other behavioral deficits, they have less available treatment options and tend to be precluded from research. An auditory marker appears well suited for the enhancement of skill-teaching in this population in that it eliminates the social features of verbal praise and is more precise than verbal reinforcement. Teaching with Acoustic Guidance or TAGteach,[1] a new behavioral intervention that uses a conditioned auditory reinforcer to mark and shape behaviors in successive approximations, was recently used to accelerate learning in a child with ASD who had difficulty learning through a traditional behavioral approach (Persicke et al., 2014). Case reports on the TAGteach webpage[2] and several case presentations at the Applied Behavioral Analysis International (ABAI) meeting have also reported that TAGteach can enhance skill acquisition rates in children with ASD who have more difficulty learning through traditional means.

Ueda (2007) demonstrated that TAGteach was effective in easing the difficulties with transitions between tasks experienced by a 3 year old with autism. After implementing TAG methodology to increase compliance with transitions, the amount of time and number of prompts decreased compared to baseline data. In a second case study of an 8 year old female diagnosed with autism, Ueda showed that TAG decreased the number of prompts and increased the level of independence in fine motor imitation skills and requesting behaviors. Also Hanson and Madden (2007) demonstrated an increase in acquisition rates for the mastery of several different target behaviors in 5 case studies with the use of TAGteach compared to the traditional operant strategies that were used in collecting baseline data. Rosenblum (2007) used TAG to teach typing to a 9-year-old male student with autism. The subject learned to type words via TAGteach with 62.3% fewer prompts than words for which TAGteach was not used. Also, Gutierrez (2007) investigated the effects of TAG on acquisition rates of imitation behaviors in two male children with autism, ages 2 and 3, following little or no progress during baseline conditions that used traditional discrete trial methods. Following 7 months of baseline data with no progress, the 3-year-old student showed 90% accuracy for two imitation responses in just 15 sessions once TAG was used. The 2-year-old student was able to acquire target behaviors in less than four TAGteach sessions following a baseline of eight sessions without TAG that showed minimal acquisition. Winkle (2007) used TAGteach with a 12 year old male diagnosed with autism to teach a social interaction by approaching a peer, getting the peer's attention, making eye contact, and saying hello. She showed that the time for the participant to perform a behavior and the average number of cues per interaction decreased while the average number of eye contact occurrences per session increased when using TAGteach. Winkle also noted improvement in the participant's affect and communication skills. Though preliminary, the aforementioned case studies, highlight the potential of TAGteach to enhance shaping procedures in children with ASD that have difficulty learning behaviors through traditional behavioral methods could prove to be highly valuable to the field.

There is a need for the empirical exploration of novel treatments that target the core deficits of autism, align themselves with prominent neuroetiological theories, and are suitable for lower functioning populations. To that end, we have combined TAGteach with NFT to bridge the gap that currently exists and completed a case series of seven children with autism and with impairments that would typically preclude them from research participation in the typical study with high functioning children.

[1] http://www.TAGteach.com

[2] http://www.TAGteach.com/Autism_And_Special_Education

The study aimed to investigate (a) whether TAGteach could be used to behaviorally prepare children to perform the skills required of an NFT intervention and EEG outcome tasks; and (b) whether electrophysiological changes or improvements in behavioral outcomes would occur in participants learning to self-regulate mu rhythms through operant strategies.

Participants were required to have a diagnosis of Autistic Disorder, be between the ages of 8 and 12, and have an IQ below 80. TAGteach was first used to shape a set of prerequisite behaviors in all participants so they could undergo an electrophysiological assessment, namely the Mu Suppression Index (MSI) and NFT thereafter. Mu suppression indices were calculated as the ratio of power during biological, goal-directed, and social action conditions relative to the power during the non-biological action condition, which is a type of movement that does not typically produce mu rhythm suppression. Following completion of pre-test measures, participants attended NFT sessions for 30–45 min 2 or 3 times per week, totaling 20 h over 20 weeks. They were trained to control power in the mu band (8–13 Hz over electrode site C4) as well as a second frequency range (43–59 Hz) recorded over C4 that reflects muscle movement artifact. A secondary auditory reinforcer, used in the TAGteach part of the study, continued to mark when participants exceeded the mu power threshold during NFT. This was followed by the primary reinforcer, which included either a videogame or preferred DVD movie that played upon mu activity exceeding a threshold. Thresholds were set based on initial individual assessment and increased when participants showed learning. Following the completion of treatment, post assessments were completed by participant and caregiver.

The results were highly encouraging in that all participants learned to perform the behaviors required of NFT and EEG outcome tasks in an average of 5 h over 6 TAGteach sessions (see **Figure 1**). The administration of NFT was entirely feasible via TAGteach in these children, providing a promising way to normalize mu suppression responses and improve behavior (see **Figure 2**). Furthermore, the results suggested that biofeedback-assisted TAGteach training could indeed help children with low functioning autism to better sustain complex skills and reduce artifact-creating behaviors for the required durations. These findings support TAGteach as a feasible method of preparing lower functioning children on the spectrum to cooperate with research tasks and participate in an otherwise inaccessible, or difficult to implement, treatment.

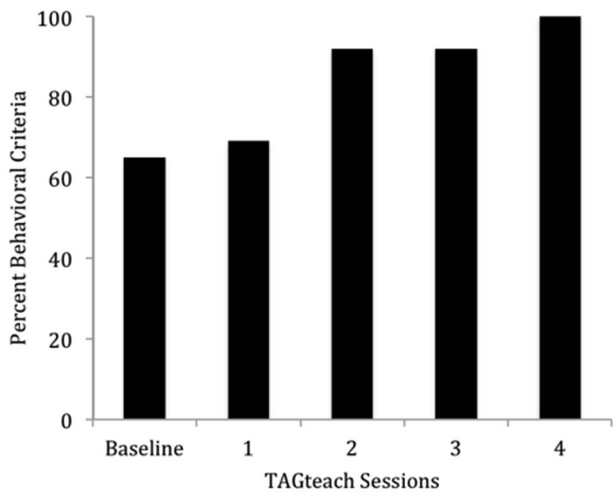

FIGURE 1 | Percent of behavioral criteria required to participate in neurofeedback training met by Case 2 across baseline and four TAGteach sessions. Cases 1–6 met 100% criteria in less than 6.25 h (M = 4.71, SD = 1.16) of training.

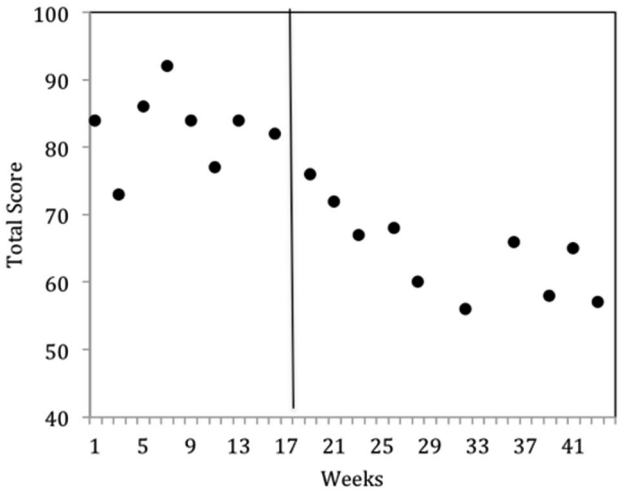

FIGURE 2 | Behavioral improvements of Case 2 at onset of neurofeedback training indicated by parent questionnaire, the Autism Treatment Evaluation Checklist (ATEC). ATEC Total scores across baseline (weeks 1–17) and intervention (weeks 18–43) phases indicated a significant improvement in mean scores. Lower ATEC scores indicate lesser severity.

CONCLUSION

There are few research studies including children on the lower end of the autism spectrum, which creates poor treatment options for this population. In this review we present TAGteach in combination with NFT as a promising alternative that may be suitable for low functioning children on the spectrum.

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Brain–computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum

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Individuals with autism spectrum disorder (ASD) show deficits in social and communicative skills, including imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors. Evidence for and against the idea that dysfunctions in the mirror neuron system are involved in imitation and could be one underlying cause for ASD is discussed in this review. Neurofeedback interventions have reduced symptoms in children with ASD by self-regulation of brain rhythms. However, cortical deficiencies are not the only cause of these symptoms. Peripheral physiological activity, such as the heart rate and its variability, is closely linked to neurophysiological signals and associated with social engagement. Therefore, a combined approach targeting the interplay between brain, body, and behavior could be more effective. Brain–computer interface applications for combined neurofeedback and biofeedback treatment for children with ASD are currently nonexistent. To facilitate their use, we have designed an innovative game that includes social interactions and provides neural- and body-based feedback that corresponds directly to the underlying significance of the trained signals as well as to the behavior that is reinforced.

Keywords: autism spectrum disorder (ASD), brain–computer interface (BCI), neurofeedback and biofeedback training, games, mirror neuron system, mu rhythm, heart rate variability, social engagement system

NEUROETIOLOGY OF AUTISM SPECTRUM DISORDER (ASD)

Autism spectrum disorder (ASD) is an increasingly prevalent condition in the U.S. with core deficits in the unique domain of human social behaviors (American Psychiatric Association, 2000; Hansen et al., 2008; Rice, 2011). Individuals with high functioning ASD show deficits primarily in social and communicative skills such as imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors. These deficits substantially impair satisfactory social interactions and prevent children from establishing adequate relations with their family or friends from their early years.

To date, no single explanation can account for the broad and varied profile of the deficits in ASD. Nonetheless, exploring the neuroetiology of this disorder is a focus of our research which was prompted by the discovery of mirror neurons. The discovery of these visuomotor cells in monkey prefrontal cortex (di Pellegrino et al., 1992) and the description of a similar network of areas in the human brain, or mirror neuron system (MNS, **Figure 1**; Rizzolatti and Craighero, 2004), has provided a testable neurobiological substrate for understanding many key concepts in human social and emotional cognition directly relevant to the behavioral and cognitive deficits observed in children with ASD (Williams et al., 2001). ASD is marked by impairments in social skills - from joint attention and the ability to comprehend actions, to learning through imitation to understanding the intentions of others (Carpenter et al., 1998; Baron-Cohen, 2009). An increasing amount of studies suggest that a dysfunction in the human MNS contributes to these kinds of social deficits (Nishitani et al., 2004; Oberman et al., 2005; Théoret et al., 2005; Dapretto et al., 2006; Hadjikhani et al., 2006; Bernier et al., 2007). Specifically, deficits are likely to arise from an inability to "form and coordinate social representations of self and others" "via amodal or cross-modal representation processes" (Rogers and Pennington, 1991), the type of function ascribed to mirror neurons. However, the theory of MNS is the object of critical debates (Enticott et al., 2013). An alternative explanation, for example, is that dyspraxia rather than the MNS could account for imitation deficits in children with ASD (Mostofsky et al., 2006; Stieglitz Ham et al., 2011). Moreover, questions have been raised as to whether the discovery of mirror neurons in monkeys can be translated to explaining human social behavior (Hickok, 2009; Turella et al., 2009).

From an anatomical perspective, an *underconnectivity* hypothesis has been proposed by Just et al. (2004), which posits that "autism is a cognitive and neurobiological disorder marked and caused by underfunctioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels." Reduced connectivity, especially in ASD individuals, is consistent across studies using various cognitive, emotional, and social tasks (Villalobos et al., 2005; Welchew et al., 2005; Just and Varma, 2007) and in both default mode and task-related functional connectivity magnetic resonance imaging (fcMRI) studies. While a

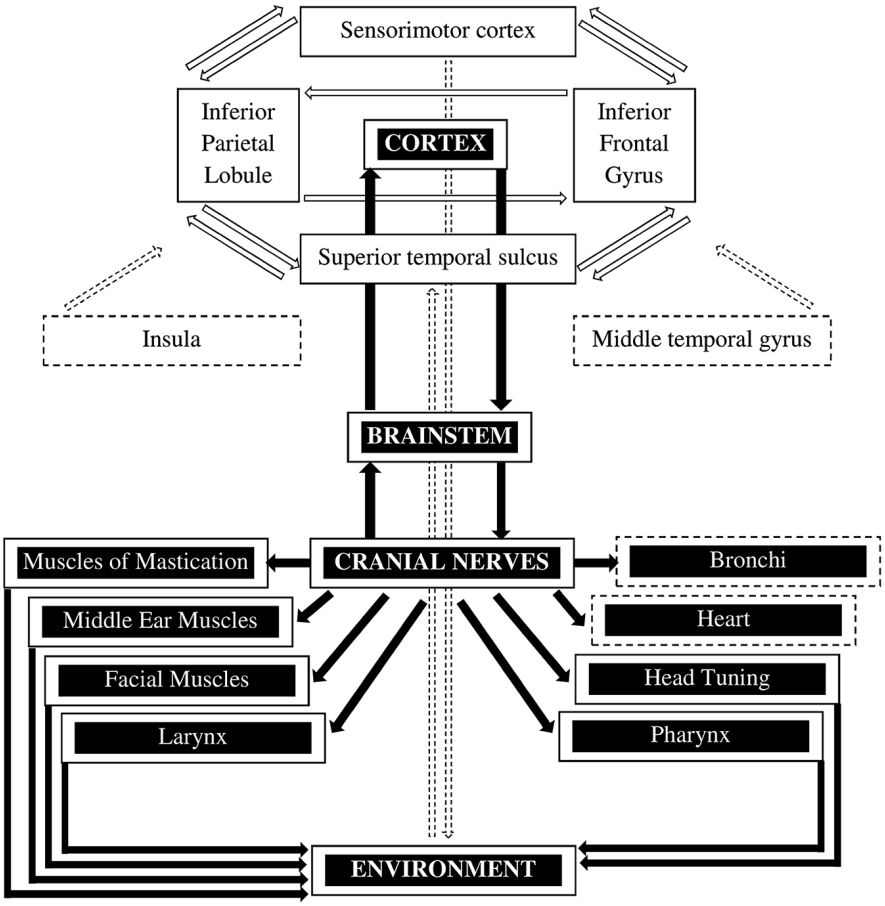

FIGURE 1 | The mirror neuron system and the social engagement system. The mirror neuron system (MNS) is represented by the white boxes with the black letters (adapted from Pineda, 2008). The core MNS (i.e., parietal frontal in the rostral cortical convexity of the inferior parietal lobule, ventral premotor area of the inferior frontal gyrus, and the superior temporal sulcus) is extended by the sensorimotor cortex as well as the insula and the middle temporal gyrus. The MNS is involved in perceiving sensory input as well as in motor output through various processes. The social engagement system is represented by the black boxes with the white letters and shows how social communication is regulated by the cortex (adapted from Porges, 2007, 2003). The solid lines indicate the somatomotor components that control the muscles of the face and the head. The dashed lines represent the visceromotor component which consists of the myelinated vagus that controls the heart and bronchi.

general theory of disordered connectivity has emerged, the nature of the disorder is not yet clear. To bring some level of reconciliation along various observations, several investigators have proposed a compromise solution that focuses on both local overconnectivity and long range underconnectivity (Anderson et al., 2011). This is not inconsistent with the MNS hypothesis since over- and under connectivity likely characterizes this specific network.

From electrophysiological studies of ASD, there is an equally emergent framework. Using phase coherence in multiple frequency bands as a measure of functional connectivity, evidence shows both global hypoconnectivity and local hyperconnectivity (Murias et al., 2007). Specifically, locally elevated coherence in the theta (3–6 Hz) frequency range in ASD subjects, particularly over left frontal and temporal regions, as well as globally lower coherence in the lower alpha range (8–10 Hz) within frontal regions was found (Murias et al., 2007). In contrast, decreased local and decreased, as well as increased, long range spectral coherences for the ASD-group in comparison to controls was reported recently (Duffy and Als, 2012). Furthermore, the coherence patterns in the ASD group were unusually stable across a wide spectral range, which was interpreted as "over-damped neural networks." Other studies have reported lower delta and theta coherences within as well as between hemispheres across the frontal region, with delta, theta, and alpha hypocoherences over temporal regions while in posterior regions, low delta, theta, and beta coherences were observed (Coben et al., 2008). Moreover, increased gamma activity over parietal cortex (Brown et al., 2005), decreased left hemispheric gamma power (Wilson et al., 2007) and increased connectivity of temporal lobes with other lobes in the gamma frequency band (Sheikhani et al., 2012) have been reported for individuals with autism. Based on the neuroanatomical, functional, and electrophysiological evidence, we hypothesize that a range of over- and underconnectivity in children with ASD, particularly in the MNS system, correlates with levels of performance in cognitive, emotional, and behavioral outcomes.

RATIONALE FOR BRAIN–COMPUTER INTERFACE (BCI) AND NEUROFEEDBACK TRAINING (NFT) FOR ASD

We have previously hypothesized that BCI-based neurofeedback using specific electroencephalographic (EEG) frequency bands should induce neuroplastic changes and lead to normalization of the MNS (Pineda et al., 2012). A BCI allows real-time information of brain activity to be fed back to a user by means of a computer in a closed loop (**Figure 2**) enabling control and natural operation of brain oscillations across cortical networks *in vivo* and in near real time (Nowlis and Kamiya, 1970; Wolpaw et al., 2002; Friedrich et al., 2009, 2013; Neuper et al., 2009; McFarland et al., 2010). The possibility of volitional control of these oscillations suggests – provided that they play a causal role in specific cognitive functions – that it is theoretically plausible that their modulation can have a functional impact.

The gold standard of neurofeedback training (NFT) is based on quantitative electroencephalography (QEEG). This approach is able to identify unique electrophysiological phenotypes (Coben et al., 2010), which makes the possibility of a QEEG-based NFT as a personalized therapeutic approach viable. That approach improves the likelihood that the intervention will be effective by first identifying activity at specific electrode sites that are outside the norm, i.e., comparing the data to already existing normative databases, and then targeting the sites of greatest difference for NFT (Cantor and Chabot, 2009; Coben and Myers, 2010; Thompson et al., 2010). Recent QEEG guided studies have reported behavioral improvements on a number of measures and it has been used to achieve behavioral and neuroregulatory improvements, primarily in children with attention deficit hyperactivity disorder, but also in those with ASD (Coben and Myers, 2010; Thompson et al., 2010). More specifically, assessment guided NFT was used to reduce hyperconnectivity in posterior-frontal to anterior-temporal regions (Coben and Padolsky, 2007). Following NFT, parents reported symptom improvement in 89% of the experimental group, with very little change in the control group. Improvement also occurred in the areas of attention, visual perceptual functioning, language, and executive functioning, with a 40% reduction in core ASD symptoms as assessed by the Autism Treatment Evaluation Checklist. There was also decreased hypercoherence in 76% of the experimental group as measured by a post-training QEEG. Kouijzer et al. (2009b) reported improved executive functions for attention control, cognitive flexibility, and planning as well as improved social behavior after a theta/beta-based NFT training in children with ASD compared to a waiting list group. The linear decrease in theta power and the increase in low beta power were hypothesized to enhance activation of the anterior cingulate cortex, which has been found to show reduced connectivity in ASD individuals (Cherkassky et al., 2006). A follow-up after twelve months revealed maintenance of the described outcomes on both executive functioning and social behavior, suggesting that NFT treatment can have long-term effects (Kouijzer et al., 2009a). The examination of physiological and behavioral data from the children themselves as well as the use of a control group and the comparison between different NFT paradigms (i.e., increase/decrease of different EEG rhythms) or between different electrode sites (i.e., occipital versus central) is crucial as parents' evaluations could be biased.

In addition to the above discussed promising NFT paradigms, research in our laboratory focus on training children on the spectrum to modulate their mu rhythm. Pineda et al. (2008, 2014) reported improvements in symptoms of autism evaluated by the parents as well as normal mu suppression after a mu-based NFT in contrast to a control group. Several studies from different laboratories have shown that mu rhythm phenomenology (alpha range: 8–13 Hz; beta range: 15–25 Hz) is linked to mirror neuron activity in that both are sensitive to movement, as well as to motor, affective, and cognitive imagery (Hari et al., 1997; Klimesch et al., 1997; Pfurtscheller et al., 1997, 2000; Muthukumaraswamy et al., 2004; Oberman et al., 2005; Pineda et al., 2008; Keuken et al., 2011). Furthermore, it was reported that mu rhythms, like mirror neurons,

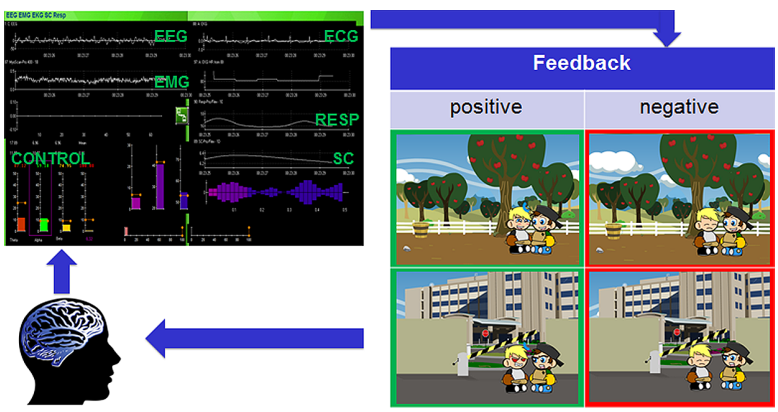

FIGURE 2 | Closed feedback loop of the Social Mirroring Game. The user's EEG and peripheral physiological measures are recorded (Thought Technology Ltd., Canada) and fed into the Social Mirroring Game which gives the user visual feedback. For positive feedback (i.e., indicated in green), the child's avatar must first approach the non-player character (NPC) and while facing him, the player has to show appropriate brain and/or peripheral physiological activity. The rewarding feedback involves the child's avatar imitating the facial emotions of the NPC. The negative feedback (i.e., indicated in red) involves the child's avatar being not responsive to the NPC. By means of the feedback, the user can learn to change his/her brain activity voluntarily and thus can control the game.

are modulated by object-directed actions (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004) and that during self-initiated, observed, and even imagined movement, mirror neuron asynchrony results in mu rhythm suppression (Pineda et al., 2000; Pineda, 2005; Neuper et al., 2009). Recently, it was demonstrated that mu rhythm suppression to movement observation is dependent on whether someone wants to be socially involved with another person and on the kind of movement observed (i.e., kinematic or goal-relevant; Aragón et al., 2013).

Both, functional magnetic resonance imaging (fMRI) and (EEG) techniques have demonstrated that mu rhythm suppression occurs in human MNS regions during tasks that activate this system, namely the inferior parietal lobe, dorsal premotor cortex, and primary somatosensory cortex (Arnstein et al., 2011). In individuals with autism, this mu rhythm suppression is not observed compared to typically developing children, supporting the role of an altered MNS (Oberman et al., 2005, 2008; Bernier et al., 2007; Oberman and Ramachandran, 2007). In contrast, Raymaekers et al. (2009) did not find a difference in mu suppression to self-executed or observed movement in autistic individuals in comparison to controls. Braadbaart et al. (2013), Arnstein et al. (2011) explained the reduced mu rhythm suppression in ASD as a more general deficit in visuomotor integration although they confirmed the relationship between mu rhythm suppression and the activation of mirror neuron areas described. In summary, although there is a lack of consensus, the majority of the literature provides enough evidence to speculate that training children to control mu rhythms may lead to functional improvements.

THE POLYVAGAL THEORY: A RATIONALE FOR COMBINING NFT AND BIOFEEDBACK FOR ASD

Cortical deficiencies might not be the only cause of ASD symptoms. Individuals with ASD show deficits in emotional responsiveness (Scambler et al., 2007). This phenomenon cannot be solely explained by specific cortical deficiencies but likely involves peripheral physiological reactions of the autonomous nervous system (Thompson and Thompson, 2009; Thompson et al., 2010). The Polyvagal Theory proposed by Porges (2003, 2007) links cortical and peripheral physiological components in the social engagement system, which is responsible for facial expression, head turning, vocalization, listening, and other socially relevant behaviors that are atypical in individuals with ASD (**Figure 1**). According to this theory, autism is associated with autonomic states that foster the misinterpretation of a neutral environment as being threatening, and consequently can change normal vagal activity and result in withdrawal from social interaction. Thus, individuals with ASD show deficits in cardiac vagal tone regulation and impaired heart rate reactivity to external stimuli (i.e., heart rate variability, HRV), which are linked to the social engagement system (Porges, 2003). Consistent with this, Thayer and Lane (2000) suggested a model of neurovisceral integration, which proposes that HRV is an index of individual differences in regulated emotional responding (Appelhans and Luecken, 2006). Moreover, recent publications argue that heart rate and its variability play an important role in emotion recognition (Quintana et al., 2012) as well as for BCI control (Kaufmann et al., 2012; Pfurtscheller et al., 2013). This suggests that training children on the spectrum to increase their vagal tone via biofeedback (Lehrer, 2007; Gevirtz, 2010, 2007) should lead to additional improvements in the social engagement system, including emotional responsiveness.

In contrast to vagal tone, which is an indicator of parasympathetic activity (Task, 1996), skin conductance is a reliable index for sympathetic arousal of the autonomous nervous system (Bach et al., 2010). While different patterns of skin conductance in individuals with ASD have been shown (Schoen et al., 2008), it is not yet clear what kind of differences occur in skin conductance and heart rate between individuals with ASD and controls (Levine et al., 2012; Mathersul et al., 2013). Therefore, more research including peripheral physiological parameters in individuals with ASD is crucial to develop a more comprehensive model of the disorder and thus produce better treatment approaches.

GAME APPLICATIONS TO COMBINE NFT AND BIOFEEDBACK INTRODUCING A NOVEL GAME PLATFORM FOR CHILDREN ON THE SPECTRUM

One treatment approach is to combine biofeedback of peripheral physiological reactions with neurofeedback of cortical electrophysiology and to do this in the context of play. Play is an ideal medium to engage children and help develop their motor skills, communication, problem solving and social skills (Oden and Asher, 1977; Hughes, 1998; MacDonald et al., 2013). There are many challenges in creating NFT and biofeedback games, not least the application must maintain player interest (Tan and Jansz, 2008) and secondly the limited genres available for ASD. The visualization of the feedback in NFT and biofeedback paradigms ranges from controlling a simple bar graph to more sophisticated visual renditions. However, the feedback typically is not related to the specific significance of the signals being trained or the anticipated behavioral changes. For example, the feedback might be the speed or response of a race car – indicating the level of control of the mu rhythm – while the anticipated outcome is that training the mu rhythm will lead to better imitation behavior. However, a specific feedback (i.e., showing the control of imitation behavior instead of a race car on the screen) for specific signals being trained (i.e., training the mu rhythm to improve imitation behavior) might be more effective in linking brain activation and anticipated behavior. Accordingly, training the EEG mu rhythm as well as training HRV should increase positive social behavior in children with ASD. Investigating this research question requires the development and implementation of a game platform that includes social interactions and specific feedback based on imitation behavior and emotional responsiveness. Therefore, we propose games such as the newly developed Social Mirroring Game (**Figure 2**), which requires children with ASD to modulate their brain activity (i.e., mu power) and/or peripheral physiological activation (e.g., increase in vagal tone) in gaming parts as well as in social situations between the child's avatar and his friend (i.e., a non-player character, NPC) in order to get rewarded. The rewarding feedback involves the child's avatar imitating the facial emotions of the NPC. The role-playing game mechanics allow the temporal dynamics of the player to be recorded to track behavior changes, accommodate game mechanic changes and to help direct the player.

For a game with the goal of improving social interactions, it is important to address the following questions: (1) is playing a social game without modulating physiological activity able to enhance appropriate social interactions? (2) is a single-person game rather antisocial than promoting social behavior? and (3) can the learned behavior be transferred from the gaming situations to the real-world?

First, it has been shown that role-play mechanism is a powerful tool towards assessing and intervening on social behaviors. Without actually manipulating brain or peripheral physiological activity, the Fearnot! social agent demonstrator (Aylett et al., 2006; Enz et al., 2008) was successful in proving that game-based platforms could have significant effect on a children population in domains related to social behavior (i.e., anti-bullying). Moreover, playing a cooperative computer game was shown to reinforce social interactions and appropriate social communicative behavior in children with ASD (Piper et al., 2006). MOSOCO (Escobedo et al., 2012) is a mobile augmented reality application based on the Social Compass curriculum (Tentori and Hayes, 2010) that facilitates practicing and learning social skills in children with ASD in social groups of neurotypical children. The results indicate that such assistive technologies with game-like interactions and role-play where points and rewards are earned improve the learning experience.

Second, the Social Motivation Adaptive Reality Treatment Games (SMART-Games; Gotsis et al., 2010) address the issue of single-player versus multiplayer games by using an avatar that exhibits different moods as an interface to a computer game which can be played as single-player, virtual or co-located multiplayer. The ECHOES project (Bernardini et al., 2014, 2012) dispels the myth that single-person games are inherently antisocial as it increases social interactions in the real world for some children with ASD.

Third, the ECHOES project also illustrates how role-play mechanics transferred to a virtual agent can be used to increase learned social skills from the game to the real world for children with ASD. The ECHOES game world, however, has no capability to adapt as its behavioral agent does not take psychophysiological inputs from a player. It is likely that brain and peripheral physiological activity is different in the video-game scenario compared to face-to-face interaction with a peer in real-life and the generalization has yet to be shown. However, like Fearnot!, ECHOES demonstrated the benefits of a game-based intervention towards social understanding, mechanisms and behavioral regulation in social situations.

In summary, games such as the Social Mirror Game are moving in the right direction and are promising tools to examine and improve the effects of training physiological measurements during social and emotional imitation behavior and interactions.

CONCLUSION

This review highlights the importance of using BCI, NFT, and biofeedback to provide novel insights about the physiological correlates of ASD, as well as the need to design innovative treatment approaches for such individuals. To date, the complex mechanisms underlying autism are not entirely understood. We propose that combining NFT and biofeedback may prove to be more effective than traditional approaches and describe a new game interface designed specifically for this purpose, i.e., to link appropriate behavior, neurophysiological and peripheral physiological reactions in social situations. As the rewarding feedback corresponds directly to the underlying significance of the signals we train as well as to the behavior we aim to reinforce and through the reinforcement of all facets of social interactions, substantial improvements in behavior, cognition and emotion can be expected for children with ASD.

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Challenges in clinical applications of brain computer interfaces in individuals with spinal cord injury

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Brain computer interfaces (BCIs) are devices that measure brain activities and translate them into control signals used for a variety of applications. Among them are systems for communication, environmental control, neuroprostheses, exoskeletons, or restorative therapies. Over the last years the technology of BCIs has reached a level of matureness allowing them to be used not only in research experiments supervised by scientists, but also in clinical routine with patients with neurological impairments supervised by clinical personnel or caregivers. However, clinicians and patients face many challenges in the application of BCIs. This particularly applies to high spinal cord injured patients, in whom artificial ventilation, autonomic dysfunctions, neuropathic pain, or the inability to achieve a sufficient level of control during a short-term training may limit the successful use of a BCI. Additionally, spasmolytic medication and the acute stress reaction with associated episodes of depression may have a negative influence on the modulation of brain waves and therefore the ability to concentrate over an extended period of time. Although BCIs seem to be a promising assistive technology for individuals with high spinal cord injury systematic investigations are highly needed to obtain realistic estimates of the percentage of users that for any reason may not be able to operate a BCI in a clinical setting.

Keywords: brain computer interface, spinal cord injury, complications, BCI performance, clinical application, neurorehabilitation

INTRODUCTION

In Europe, an estimated number of 330,000 people are living with the consequences of spinal cord injury (SCI), with 11,000 new injuries occurring per year (Ouzký, 2002; van den Berg et al., 2010). Numbers for the United States are in the same range (National Spinal Cord Injury Statistical Center, 2012). Despite marked regional differences across the globe, there has been a trend toward increasing prevalence rates of SCI over the past decades (Furlan et al., 2013). While the most frequent causes of SCI continue to be traffic, work-related and sporting accidents, in industrial countries there is an ongoing trend toward a higher proportion of non-traumatic lesions (Exner, 2004). As a consequence, the average age of persons at the time of injury is steadily increasing (National Spinal Cord Injury Statistical Center, 2012). Depending on its severity the SCI leads to restrictions up to the complete loss of motor, sensory and autonomic functions below the level of injury. Currently, ∼55% of all individuals with an SCI are tetraplegic due to injuries of the cervical spinal cord with resulting life-long paralysis of the lower and upper extremities. The majority of tetraplegic patients (∼28%) have a neurological level of lesion at C4 and C5 at the time of discharge from acute care to rehabilitation facilities (National Spinal Cord Injury Statistical Center, 2012). In lesions at the level of C5, finger function is typically impaired, while in most C4 lesions, hand function and elbow flexion are additionally limited. About 8% of the patients have a neurological level rostral to C4 resulting in the loss of motor functions of both upper extremities including shoulder, elbow, and hand movements. These individuals lose their independence and privacy almost completely, which results in a tremendous decrease in quality of life.

MEDICAL CONSEQUENCES OF SCI IN THE ACUTE PHASE

A SCI results in impairments of motor, sensory and autonomic functions below the lesion. The degree of initial impairment and the potential for neurological recovery is mainly determined by the severity and location of the lesion.

The first weeks after the injury patients are in the phase of the spinal shock, i.e., that no tendon tap reflexes and flaccid muscle tones are present. The spinal shock typically ends within the first 2 weeks after onset of SCI with reappearing tendon reflexes and muscle tone. After spinal shock spasms, i.e., involuntary muscle contractions that cannot be suppressed or controlled by the patient, as clinical signs of spasticity slowly show up (Hiersemenzel et al., 2000). Spasticity may result in abnormal joint positions and later in joint contractures in particular if motor neurons of antagonistic muscles have been damaged. An example is a fixed elbow joint in fully flexed position after a C4 lesion with a hyperactive biceps and a completely paralyzed triceps muscle.

A variety of autonomic dysfunctions develop after an SCI including paralysis of the bladder and bowel and orthostatic hypotension due to venous pooling of the blood in the paralyzed legs. In individuals with lesions at or above the level of the fourth thoracic spinal segment additional cardiovascular complications such as low systolic and diastolic blood pressure, bradycardia, and autonomic dysreflexia (AD) are present. After spinal shock ends

spastic activity may develop in the detrusor muscle restricting the bladder capacity to store urine and resulting in incontinence.

In very high cervical lesions above the level of C3 respiratory problems are present due to impaired voluntary control of the diaphragm. This applies in particular to patients in the acute phase, during which 6.5% of all patients are respirator dependent in the first weeks after injury for at least some hours a day (National Spinal Cord Injury Statistical Center, 2012).

Rehabilitation starts on the first day after the injury. After cervical SCI patients are in need of assistive technology for control of devices such as computers, wheelchairs or environmental control systems. The therapeutic regimes applied in this early phase of rehabilitation mainly focus on restoration of impaired motor functions by inducing spinal and supraspinal neuroplasticity.

PERSISTENT IMPAIRMENTS IN CHRONIC SCI

The highest degree of neurological recovery occurs within the first 3 months after injury, while functional recovery is delayed to up to 6–12 months (Curt et al., 2008). People with an initial sensorimotor complete [ASIA Impairment Scale A (Waring et al., 2010)] lesion have the lowest potential for substantial neurological and functional recovery, while initially motor incomplete patients have a high probability to regain a relevant ambulatory function. The bilateral loss of the grasp function in individuals suffering from a cervical SCI severely limits the affected individuals' ability to live independently and retain gainful employment post injury. Therefore, one of the main priorities of these patients is to improve a missing grasping and reaching function (Anderson, 2004; Snoek et al., 2004; Collinger et al., 2013). If there is sufficient voluntary control of muscles distal to the elbow, surgical procedures such as muscle and tendon transfers, tenodesis and arthrodeses, can be successfully applied for regaining a meaningful grasp function (Hentz and Leclercq, 2002; Keith and Peljovich, 2012). However, if no voluntary motor functions distal to the elbow joint are present or an individual is unwilling to undergo surgery with the associated extended post-surgical rehabilitation period, grasp neuroprostheses on the basis of functional electrical stimulation (FES) may represent a valid alternative for restoring upper extremity function (Rupp and Gerner, 2007). If motor impairments persist, they may lead to negative secondary complications that restrict the successful application of grasp neuroprosthesis. Immobility may lead to a reduction in the passive range of motion of affected joints, which may result in severe contractures with totally immobile joints due to calcified joint capsules. Adequate physical therapy may prevent some of these negative side effects on the musculoskeletal body structures. If no voluntary movements are preserved in the upper extremities no restorative approaches are currently available. To compensate for the loss of motor function and to allow individuals with severe disabilities to participate in society, assistive devices are used enabling environmental control and computer, internet, and social media access. The latter is extremely important for end users with severe motor impairments, because in the virtual world persons with handicaps are on the same level than non-impaired people. Examples for assistive devices used for this purpose are – depending on the residual capabilities of the end user – joysticks for the hand or the chin, suck-and-puff control, voice control, or eye-tracking systems. In very high lesioned patients and particularly those depending on artificial ventilation the input devices for setup of an electronic user interface are in general very limited and may not work with a sufficient level of performance over an extended period of time. Therefore, over the last decade BCIs have become an interesting option for end users who achieve only a moderate level of control with traditional input devices.

BRAIN COMPUTER INTERFACES

Brain computer interfaces (BCIs) are technical systems that provide a direct connection between the human brain and a computer (Wolpaw et al., 2002). These systems are able to detect thought-modulated changes in electrophysiological brain activity and transform the changes into control signals. A BCI system consists of four sequential components: (1) signal acquisition, (2) feature extraction, (3) feature translation, and (4) classification output, which interfaces to an output device. These components are controlled by an operating protocol that defines the onset and timing of operation, the details of signal processing, the nature of the device commands, and the oversight of performance (Shih et al., 2012).

TECHNOLOGY AND BRAIN SIGNALS OF BCI SYSTEMS FOR CLINICAL APPLICATIONS

Although, all implementations of BCIs build upon the same basic components, they differ substantially in regard to complexity of the technology for acquisition of brain signals, their basic mode of operation (cue-based, synchronous vs. asynchronous) and the underlying physiological mechanisms (Birbaumer et al., 2008; Riccio et al., 2012). For application in the clinical environment non-invasive, small scale systems represent the only realistic option. Most of the non-invasive BCI systems rely on brain signals that are recorded by electrodes on the scalp [electroencephalogram (EEG)]. Another option for practically usable BCIs are systems based on near-infrared spectroscopy (NIRS; Strait and Scheutz, 2014).

Near-infrared spectroscopy uses the fact that the transmission and absorption of near-infrared light in human body tissues contains information about hemoglobin concentration changes. When a specific area of the brain is activated, the localized blood volume in this area changes rapidly. Optical imaging can measure the location and activity of specific regions of the brain by continuously monitoring blood hemoglobin levels through the determination of optical absorption coefficients.

In contrast to NIRS, EEG-based BCI systems can function in most environments with relatively inexpensive equipment and therefore offer the possibility of practical use in either the clinical setting or later in end users' homes. A variety of EEG signals have been used as measures of brain activity: event-related potentials (ERPs; Farwell and Donchin, 1988; Sellers and Donchin, 2006a; Nijboer et al., 2008), frequency oscillations particularly the EEG sensorimotor rhythms (SMRs; Pfurtscheller and Lopes da Silva, 1999; Wolpaw et al., 2000), slow cortical potentials (SCPs; Birbaumer et al., 1999; Neumann et al., 2003), and steady-state responses (SSRs; Cheng et al., 2002). EEG-based BCIs can be categorized into endogenous, asynchronous and exogenous,

synchronous systems. Asynchronous BCIs depend on the users' ability to voluntary modulate their electrophysiological activity such as the EEG amplitude in a specific frequency band. In asynchronous BCIs the time point for changes of the control signals is not predefined by the system, but the user is free to initiate decisions at any time. These systems usually require a substantial amount of training. Examples for this class of BCIs are systems based on the detection of SMRs or SCPs. Synchronous BCIs depend on the electrophysiological activity evoked by external stimuli and do not require intensive training. The most common synchronous BCI is based on P300 ERPs. Although systems based on steady-state evoked potentials (SSEPs) such as steady-state visual evoked potentials (SSVEPs) or steady-state somatosensory evoked potentials (SSSEPs) combine components of asynchronous and synchronous approaches, the introduction of cues improves their accuracy. Depending on the brain signals used for operation BCIs greatly vary in regard to the minimal and typically used number of electrodes, training times, accuracies, and typical information transfer rates (for overview see **Table 1**; Birbaumer et al., 2003; Hinterberger et al., 2004; Guger et al., 2012a; Combaz et al., 2013).

BCIs based on slow cortical potentials

Slow cortical potentials are slow voltage changes generated on the cerebral cortex, with a duration varying between 300 ms and several seconds. Negative SCPs are typically associated with movement and other functions that imply cortical activity. It has been demonstrated that people are able to self-regulate these potentials and use these modulations for control of assistive devices like a spelling device (Rockstroh et al., 1984). By this, an alternative communication channel was provided to totally paralyzed patients. However, with SCP-based BCIs only a very low information transfer rate of typically less than one letter per 2 min can be achieved (Birbaumer et al., 1999). Additionally, a substantial amount of training, during which patients receive feedback about their EEG-activity, is necessary to achieve a sufficient level of control. Therefore, SCP-based BCIs do not represent the first choice for providing individuals with high SCI with a communication or control interface in the acute phase after the injury.

BCIs based on sensorimotor rhythms

Another type of EEG-based BCI exploits the modulation of SMRs. These rhythms are oscillations in the EEG occurring in the alpha (8–12 Hz) and beta (18–26 Hz) bands and can be recorded over the primary sensorimotor areas on the scalp. Their amplitude typically decreases during actual movement and similarly during mental rehearsal of movements [motor imagery (MI); Pfurtscheller and Lopes da Silva, 1999; Neuper et al., 2005]. Several studies have shown that people can learn to modulate the SMR amplitude by practicing MIs of simple movements, e.g., hand/foot movements (Kaiser et al., 2014; Toppi et al., 2014). This process occurs in a closed-loop, meaning that the system recognizes the SMR amplitude changes evoked by MI and these changes are instantaneously fed back to the users. This neurofeedback procedure and mutual human–machine adaptation enables BCI users to control their SMR activity and use these modulations to control output devices in an asynchronous manner (Pineda et al., 2003; Cincotti et al., 2008).

For a typical 2-class SMR-BCI different paradigms of MIs such as one hand vs. feet or left vs. right hand are used either in a switch based fashion by introduction of a threshold or in an analog manner by directly connecting the classifier output to the output device. An often underestimated problem in practical applications of BCIs and in particular of SMR-based BCIs is the detection of a non-intention condition, during which a user does not want to send any command (zero-class). This so called zero-class problem is often handled in brain-switch implementations by defining one MI class as the resting class or to use long MIs to pause or reactivate the system (Pfurtscheller et al., 2003; Rohm et al., 2013). However, this approach is not appropriate for all applications, which renders the zero-class problem as one of the major limiting factors for practical use of BCIs.

Motor imagery-brain computer interfaces offer further possibilities in the context of neurorehabilitation of spinal cord injured patients that go beyond the traditional use for control of assistive device. After a SCI substantial functional brain reorganization occurs that plays a critical role for functional recovery and may have pathological consequences (Nardone et al., 2013). The basis for a therapeutic use of BCIs is formed by the fact that the central nervous system shows a life-long ability for neural plasticity, which can be enhanced after a trauma or injury by task-specific training (Dietz and Fouad, 2014). The key elements for an effective neurorehabilitative training based on motor learning are voluntarily triggered movement intentions and a synchronized sensory and proprioceptive feedback of the limbs' motor actions. BCIs hold promise to enable the detection of

Table 1 | Types of EEG-based BCIs suitable for application in patients in the acute phase after SCI together with their main characteristics.

Parameter BCI	Minimal (typical) number of electrodes	Training time	Population with 90–100 (below 80) accuracy without training (%)	Typical rate of decisions/min
SMR (2-class)	4 (10) + 1 reference	weeks to months	6 (81)	4 Bits/min
SCP	1 (1) + 2 reference	weeks to months	33 with accuracy above 70	<1 Bit/min
P300	3 (9) + 1 reference	minutes to <1 h	73 (11)	10 Bits/min
SSVEP	6 + 1 reference	minutes to <1 h	87 (4)	12 Bits/min

An overview of the most common practical types of BCIs together with their minimal number of electrodes, a qualitative estimation of typical training times and their typical accuracy and bit rate is provided. A common ground electrode, which is needed for all BCIs, is not explicitly mentioned.

intended movements, e.g., the hand, even in high spinal cord injured patients, making them an ideal tool for closed-loop neurorehabilitative therapies when used in combination with grasping and reaching neuroprosthesis (Jackson and Zimmermann, 2012; Rupp et al., 2013; Savic et al., 2014). Additionally, by practicing feedback-controlled MI of paralyzed limbs the integrity of cortical neuronal connections may be preserved or neurological recovery of motor function may be even enhanced (Kaiser et al., 2014).

BCIs based on event-related potentials

Event-related potential-based BCIs make use of the fact that specific neural activity is triggered by and involved in the processing of specific events. These systems are implemented with an oddball paradigm, wherein a rare target (oddball event) is presented within frequent non-target events. These BCIs usually exploit an endogenous ERP component, known as P300, as input signal. The P300 is a positive deflection in the EEG occurring 200–500 ms after the presentation of the rare visual, auditory or somatosensory stimulus and is a reliable, easy to detect ERP (Sutton et al., 1965). By focusing attention on the rare target, e.g., by keeping a mental count of its occurrence, the P300 amplitude can be increased and therefore its detection and classification improves (Kleih et al., 2011). In individuals with SCI eye-gaze is preserved and thus a visual rather than an auditory oddball paradigm is the preferred choice, because the information transfer rate and accuracy is substantially higher and perceived workload much lower in visual P300-based BCIs (Furdea et al., 2009; Halder et al., 2010; Kathner et al., 2013). The big advantage of P300 compared to SMR-based BCIs is that they can be operated with almost no setup time in 99% of the general population (Guger et al., 2009b). Although, P300-BCIs basically work without electrodes on the occipital cortex, their performance can be improved, if electrodes on the posterior head region are used (Krusienski et al., 2008). Special care must be taken that these electrodes do not cause any discomfort in acute patients with high SCI lying in bed and resting their heads on a pillow or using a head-rest.

BCIs based on steady-state evoked potentials

Steady-state evoked potentials are stable oscillations that can be elicited by rapid repetitive (usually > 6 Hz) visual, auditory, and somatosensory stimuli. The most common type of SSEP-based BCI are the SSVEP-based BCIs, where screen objects flickering at different frequencies are visually presented to subjects. Focusing their attention to the intended stimulus elicits enhanced SSVEP responses at the corresponding frequency, which can be detected, classified and translated into control commands (Vialatte et al., 2010). SSVEP-based BCIs have the advantages of a high information transfer rate, practically no training time, and they work in almost every user (Allison et al., 2010; Guger et al., 2012a). SSVEPs are recorded over occipital brain areas and the same caution has to be taken like in some P300-based systems to avoid any discomfort caused by electrodes on the back of the head.

A relatively new approach in BCI is the use of auditory steady-state responses (ASSR), where the user can modulate the ASSR by selective attention to a specific sound source such as tone burst trains with different beat frequencies on the left and right ear (Kim et al., 2011). The frequency of the tone, on which a user is putting attention to, can be registered in the EEG and further used to generate a switch signal. Nevertheless, BCIs based on visual evoked potentials are the preferred choice in individuals with SCI that have unimpaired visual function, because the information transfer rate of ASSR-based BCIs is tenfold lower than of SSVEP-based systems (Baek et al., 2013).

The limitations of the placement of electrodes in the posterior region of the skull may be overcome in BCIs based on SSSEPs (Muller-Putz et al., 2006), which record EEG activity over the sensorimotor cortex of the midbrain. In SSSEP-based BCIs tactile stimulators on both hands are used to induce "resonance"-like frequencies in the somatosensory cortex. Users can be trained to modulate these SSSEPs, thereby generating binary control signals. Although they represent an exciting alternative to traditional BCI approaches, SSSEP-based BCIs are in general not applicable in patients with high SCI due to the impairment of sensory functions present in all limbs.

HYBRID BCIs

A novel development in BCI research is the introduction of the hybrid BCI (hBCI) concept (Müller-Putz et al., 2011). A hBCI consists of a combination of several BCIs or a BCI with other input devices (Allison et al., 2012). These input devices may be based on the registration of biosignals other than brain signals, such as electromyographic activities. Using this approach, a user can generate a single command signal either by fusing different input signals or by simply selecting one of them (Müller-Putz et al., 2011). In the latter case, the input signals can be dynamically routed based on their reliability, i.e., continuously monitoring the quality, and the input channel with the most stable signal will then be selected (Kreilinger et al., 2011). In the case of signal fusion, each of the input signals contributes to the overall command signal with a dedicated weighting factor (Leeb et al., 2011). These factors are generally not static, but can be dynamically adjusted in accordance with their reliability, which is quantified by appropriate quality measures. The hBCI is fully compliant with the user-centered design concept (ISO, 2010). The key message of this approach is that the technology has to be adapted to the individual users' ability and needs and not vice versa. Combining BCIs with established user interfaces may allow more end users to control assistive technology or may simplify the use of existing devices. However, this extension of the target population comes with the drawback that longer preparation times are needed for setup of the additional components of the hBCI. From the users' perspective it is important to carefully evaluate the design of the hBCI's control scheme and not to cause additional mental workload. Control schemes based on a sequential control task of the different input signals are – at least at the beginning of the training – superior to those, for which a user must control different input signals simultaneously. With practice users might learn to perform multiple tasks, thereby making full use of the hBCI approach.

In any case, the hBCI concept helps to overcome limitations inherent to a singular BCI system, e.g., false-positive, unintended decisions or the zero-class problem. In fact the second input

signal can be effectively used to indicate an "idling" state or to introduce a context-specific correction mechanism. An example for demonstration of the superiority of this approach is an hBCI-controlled telepresence robot, where the user navigates to the left and right by imagination of movements of the left and right hand and stops/starts the movements of the robot by an electromyographic switch activated by a short muscle twitch (Carlson et al., 2013). In an hBCI controlled communication application based on two BCIs (P300 and SSVEP) SSVEP activity is used to assess whether the subject is focused on a spelling task. If no SSVEP activity is found, then the system assumes that the user is not paying attention to the spelling system and does not output any characters (Panicker et al., 2011). Another example is an hBCI-controlled reaching and grasping neuroprosthesis, in which the hBCI consists of an SMR-BCI combined with an analog shoulder joystick (Rohm et al., 2013). The neuroprosthesis is activated/deactivated by a long MI detected by an SMR-BCI and the degree of hand closing/elbow flexion is controlled by shoulder movements. To prevent an unintended deactivation of the system several context-specific plausibility checks were implemented in the control concept, e.g., deactivation is not allowed, if the hand is closed or if the shoulder is moved. In another example of an hBCI-controlled computer interface based on an SMR-BCI and a mouth mouse, a brain-switch simulating a double-click can only be generated while the mouse cursor is not moving (Faller et al., 2012). This comprehensive list of examples shows that the hBCI concept is a valuable extension of traditional BCI approaches and represents a big step forward toward the regular use of BCIs as assistive devices.

APPLICATION OF BCIs IN END USERS WITH MOTOR IMPAIRMENTS

Most of the results in BCI research have been obtained involving healthy subjects, in particular students working in research labs due to their easy availability and intrinsic motivation to participate in experiments designed and set up by their own (Moghimi et al., 2013). Only a low percentage (estimated <5%) of BCI studies involved end users with a real need for a BCI, most of them end users with amyotrophic lateral sclerosis (ALS) in the so-called locked-in-state with no motor functions preserved except eye movements (Pasqualotto et al., 2012). All BCI research in end users with SCI was carried out so far with individuals in the chronic stage. This means, that they were participating in studies at the earliest 1 year after the onset of the injury in a stable neurological, psychological, and social state.

BCIs for communication

Nowadays, researchers mostly work with the P300 signal for communication purposes. Numerous clinical studies confirm the efficacy of the P300-BCI in paralyzed patients with four choice responses, e.g., "Yes/No/Pass/End" (Sellers and Donchin, 2006b) or "Up/Down/Left/Right" for cursor movement (Piccione et al., 2006; Silvoni et al., 2009). With P300-spellers words could be composed letter by letter, which are arranged in a matrix fashion in rows and columns. One letter is selected by implementation of an oddball paradigm, in which rows and columns are highlighted randomly while the user focuses on one specific letter (target letter) she or he wishes to spell and tries to ignore all other letters that are highlighted in other rows or columns (non-target letters). Each time the target letter is highlighted, a P300 signal occurs in the frontoparietal brain region. Each target letter can be identified by a classifier, which detects the occurrence a P300 signal every time the row and column of the intended letter is highlighted and selects the letter accordingly. In a recent study a new paradigm was recently introduced for enhancement of the P300 control (Kaufmann et al., 2013), in which a famous face – in this case the face of Albert Einstein is superimposed – on top of the matrix display. By the implementation of this paradigm persons formerly unable to control a traditional P300-based speller were enabled to successfully use this kind of communication interface.

An alternative to P300 based spellers are SMR-based spelling systems such as the Hex-o-Spell paradigm (Blankertz et al., 2006). In the Hex-o-Spell paradigm hexagons filled with groups of letters or a single letter are arranged in a circular fashion with a pointing arrow in the center of the circle. The circle can be rotated by one type of MI, e.g., right hand movements, and extended for selection with another MI, e.g., foot movements.

Although, the traditional matrix-based P300-based spellers are the most widespread type of BCIs used for communication purposes, alternative BCIs using different designs and signal modalities such as SSVEPs are developed to build a faster, more accurate, less mentally demanding, and more satisfying BCI (Combaz et al., 2013). Such systems are not only beneficial in end users in a locked-in state, but may also enable basic communication in individuals with very high SCI, who are ventilator dependent. However, this needs to be proven in future clinical studies.

BCIs for wheelchair and environmental control

Being mobile is beside communication and manipulation an essential need of motor impaired end users. Wheelchairs represent a very important assistive device to enable mobility in individuals with SCI. Persons with severe motor disabilities are dependant on electrical wheelchairs controlled by hand- or chin-operated manual joysticks. If not enough residual movements are present, eye-gaze or suck-and-puff control units may serve as a wheelchair user interface. Suck-and-puff control is mainly based on four types of commands. If air is blown into/sucks from the device with high pressure/vacuum, the controller interprets this as a forward/backward drive signal. If a low pressure or vacuum is applied, the wheelchair drives right or left. With this rather simple control scheme users are able to perform most navigation tasks with their wheelchair. Though the thresholds for low/high pressure are individually calibrated, the end user must be able to reliably generate two different levels of air pressure/vacuum over a sustained period of time to achieve a good level of control. Since these prerequisites are not present in all very high lesioned spinal cord injured people, BCIs may represent an alternative control option.

At the current state of the art all types of non-invasive BCIs are providing only a limited command rate and are insufficient for dexterous control of complex applications. Thus, before the successful application of control interfaces with low command rates – including BCIs – in mobility devices intelligent control

schemes have to be implemented. Ideally, the user only has to issue basic navigation commands such as left, right and forward, which are interpreted by the wheelchair controller integrating contextual information obtained from environmental sensors. Based on these interpretations the wheelchair would perform intelligent maneuvers including obstacle avoidance and guided turnings. In conclusion, in such a control scheme the responsibilities are shared between the user, who gives high-level commands, and the system, which executes low-level interactions with more or less degree of autonomy. With this so called shared control principle researchers have demonstrated the feasibility of mentally controlling complex mobility devices by non-invasive BCIs, despite its slow information transfer rate (Flemisch et al., 2003; Vanhooydonck et al., 2003; Carlson and Demiris, 2008).

Although asynchronous, spontaneous BCIs like SMR-based BCIs seem to be the most natural control option for wheelchairs, there are a few applications using synchronous BCIs (Iturrate et al., 2009; Rebsamen et al., 2010). Like in most communication applications these BCIs are based on the detection of the P300 potential evoked by concentrating on a flashing symbol in a matrix. For wheelchair control the system flashes a choice of predefined target destinations several times in a random order and finally the stimulus that elicits the largest P300 is selected as the target. Afterward the intelligent wheelchair drives to the selected target autonomously. Once there it stops and the subject can select another destination. The fact that the selection of a target takes ∼10 s and that the user intent is only determined at predefined time points takes the usability of cue-based BCIs for control of mobility devices into question.

In BCI-controlled mobility devices developed in the framework of recent European projects MAIA and TOBI the users' mental intent was estimated asynchronously and the control system provided appropriate assistance for wheelchair navigation. With this approach the driving performance of the BCI controlled device greatly improved in terms of continuous human–machine interaction and enhanced practicability (Vanacker et al., 2007; Galán et al., 2008; Millán et al., 2009; Tonin et al., 2010). In the most recent approach of shared control the user asynchronously sends – with the help of a MI based BCI – high-level commands for turning left or right to reach the desired destination. Short-term low-level interaction for obstacle avoidance is done by the mobility device autonomously. In the applied shared control paradigm the wheelchair pro-actively slows down and turns for avoidance of obstacles as it approaches them. For provision of the latter functionality the wheelchair is equipped with proximity sensors and two webcams for obstacle detection (Borenstein and Koren, 1991; Carlson and Millán, 2013). Cheap webcams were used instead of an expensive laser range-finder to provide an affordable solution, in which the additional equipment for implementation of the shared control does not cost more than the wheelchair itself.

Although a lot of literature is available on the technical specifications of BCI-controlled wheelchairs, only a few studies involving end users are available (Nguyen et al., 2013) and even less involving end users in real need of a BCI.

In the early phase of rehabilitation patients with a cervical spinal injury may not be cardiovascular stable. Therefore, wheelchair mobilization may be difficult and other ways to provide some form of independence and social inclusion need to be found. Access to computers in general and to the internet and social media in particular is an important goal for patients to communicate with their relatives and friends. For this purpose, P300-based BCIs may offer a quick way to setup an interface for assessing traditional social media like Twitter or moving avatars in virtual reality environments like Second Life (Fazel-Rezai et al., 2012). However, the preliminary results obtained in experiments with non-motor impaired persons need to be confirmed in paralyzed end users.

Another important issue is to allow severely paralyzed patients to control their environment independently, to which BCIs-controlled environment control systems may contribute significantly. First results in end users with handicaps show that environmental control by an asynchronous P300 BCI is possible. However, system testing also revealed that the minimum number of stimulation sequences needed for correct classification had a higher intra-subject variability in end users with respect to what was previously observed in young, non-disabled controls (Aloise et al., 2011). Also special focus must be put on the design of the visual control interface to achieve high accuracy while keeping mental effort low (Carabalona et al., 2012). A major progress can be expected in respect to the availability of enhanced BCI-controlled computer and social media access and environmental control from the European projects BrainAble and BackHome.

BCIs for control of upper extremity neuroprosthesis

Today, the only possibility of restoring permanently restricted or lost functions to a certain extend in case of missing surgical options (Hentz and Leclercq, 2002) is the application of FES. Over the last 20 years FES systems with different level of complexity were developed and some of them introduced into the clinical environment (Popovic et al., 2002). These systems deliver short current impulses eliciting physiological action potentials on the efferent nerves, which cause contractions of the innervated, yet paralyzed muscles of the hand and the forearm (van den Honert and Mortimer, 1979). On this basis FES artificially compensates for the loss of voluntary muscle control.

When using the FES in a compensatory setup at a very early stage of primary rehabilitation the easiest way of improving a weak or lost grasp function is the application of multiple surface electrodes. With only seven surface electrodes placed on the forearm two grasp patterns, namely lateral grasp and palmar grasp, can be restored (Rupp et al., 2012). With the combination of surface electrodes and a finger synchronizing orthosis the difficulties with daily reproduction of movements and huge variations of grasp patterns depending on wrist rotation angle may be overcome (Leeb et al., 2010).

Through the last decade it has become obvious that the user interface of all current FES devices is not optimal in the sense of natural control, relying on either the movement or the underlying muscle activation from a non-paralyzed body part to control the coordinated electrical stimulation of muscles in the paralyzed limb (Kilgore et al., 2008; Moss et al., 2011). In the case of individuals with a high, complete SCI and the associated severe disabilities not

enough residual functions are preserved for control. This has been a major limitation in the development of a reaching neuroprostheses for individuals with a loss not only of hand and finger but also of elbow and shoulder function.

Several BCI approaches mainly based on SSVEPs have been introduced as a substitute for traditional control interfaces for control of an abdominal FES system (Gollee et al., 2010), a wrist and hand orthosis (Ortner et al., 2011) or a hand and elbow prosthesis (Horki et al., 2010).

Apart from those simple approaches, BCIs have enormous implications providing natural control of a grasping and reaching neuroprosthesis control in particular in individuals with a high SCI by relying on volitional signals recorded from the brain directly involved in upper extremity movements.

In Pfurtscheller et al. (2003) a pioneering work showed for the first time that a MI-BCI control of a neuroprosthesis based on surface electrodes is feasible. In this single case study the restoration of a lateral grasp was achieved in a tetraplegic subject, who suffers from a chronic SCI with completely missing hand and finger function. The end user was able to move through a predefined sequence of grasp phases by imagination of foot movements detected by a brain-switch with 100% accuracy. He reached this performance level already prior to the experiment by some months of training with the MI-BCI (Pfurtscheller et al., 2003) and has maintained it for almost a decade by regular continuation of the training (Enzinger et al., 2008).

A second feasibility experiment has been performed, in which a short-term BCI-training has been applied in another individual with tetraplegia. This subject was using a Freehand system for several years. After 3 days of training the end user was able to control the grasp sequence of the implanted neuroprosthesis with a moderate, but sufficient performance (Müller-Putz et al., 2005).

In these first attempts the BCI was rather used as a substitute for the traditional neuroprosthesis control interface than as an extension. With the introduction of FES-hybrid orthoses it becomes more important to increase the number of independent control signals. With the recent implementation of the hBCI framework it became feasible to use a combination of input signals rather than BCI alone. In a first single case study a combination of a MI-BCI and an analog shoulder position sensor is proposed (Rohm et al., 2013). By upward/downward movements of the shoulder the user can control the degree of elbow flexion/extension or of hand opening/closing. The routing of the analog signal from the shoulder position sensor to the control of the elbow or the hand and the access to a pause state is determined by a digital signal provided by the MI-BCI. With a short imagination of a hand movement the user switches from hand to elbow control or vice versa. A longer activation leads to a pause state with stimulation turned off or reactivates the system from the pause state. With this setup a highly paralyzed end user, who had no preserved voluntary elbow, hand and finger movements, was able to perform several activities of daily living, among them eating a pretzel-stick, signing a document and eating an ice cone, which he was not able to perform without the neuroprosthesis.

CLINICAL APPLICATIONS OF BCIs

In the clinical setting the main focuses of BCIs in patients with an acute or subacute SCI in the first months after injury are (1) the compensation of a temporarily or permanently impaired motor function, preferably if simpler techniques do not allow for a sufficient control of assistive devices, and (2) the maintenance of cortical connectivity for avoidance of maladaptive plasticity with symptoms like neuropathic pain and enhancement of functional recovery by induction of beneficial neuroplasticity (Grosse-Wentrup et al., 2011). Almost all patients with substantial motor impairments are potential candidates for neurofeedback, i.e., receiving feedback on neural cortical states, and neurorehabilitative therapies, e.g., BCI-controlled FES (Birbaumer et al., 2009). Unfortunately, the empirical evidence for a positive impact of BCI technology for therapeutic purposes is scarce and clinical studies are urgently needed to provide evidence for their added value.

For compensation of motor impairments the preferred target population is the group of high lesioned, tetraplegic patients with severe motor impairments in particular of the upper extremities, who may be temporarily ventilator dependent and have limited ability to speak due to the use of a tracheal tube. Most of the BCI research related to communication and control in end users with disabilities has been carried out with individuals in the chronic stage meaning that most of the people returned to their homes, were in a stable neurological and psychological condition and their family members or caregivers were properly instructed to correctly setup and operate a BCI. In contrast to this the condition of the patients and the environment is very different in the clinical setting, which presumably affect the users' (end users and caregiver) priorities (Huggins et al., 2011).

The aim of the following chapter is to provide an overview of factors that may limit the successful implementation of BCIs for control of assistive devices or for neurorehabilitation in the clinical setting.

FACTORS LIMITING THE CLINICAL APPLICATION OF BCIs

A couple of aspects have prevented BCIs so far from being regularly used as a user interface for control of assistive devices or as an adjunct therapeutic tool in the clinical setting of the rehabilitation of acute spinal cord injured patients. These limiting factors are mainly related to three distinct domains: (1) Problems and limitations of the available technology for signal acquisition and processing, (2) user-specific factors such as medication or personal user characteristics, and (3) infrastructure and health-care related constraints (**Figure 1**).

HARDWARE AND TECHNOLOGY RELATED FACTORS

Today, commercial BCI systems are mainly based on gel electrodes placed inside an EEG cap. The correct montage of the cap and the electrode on the skull under the premise of a proper electrode contact are very time-consuming procedures taking in the case of eight electrodes an experienced therapist up to 15–20 min. With the use of more expensive active electrodes, which integrate the amplifier in the electrode, the montage time can be substantially reduced. However, if electrode gel is used, the hair of the end user needs to be washed afterward. This puts additional burden

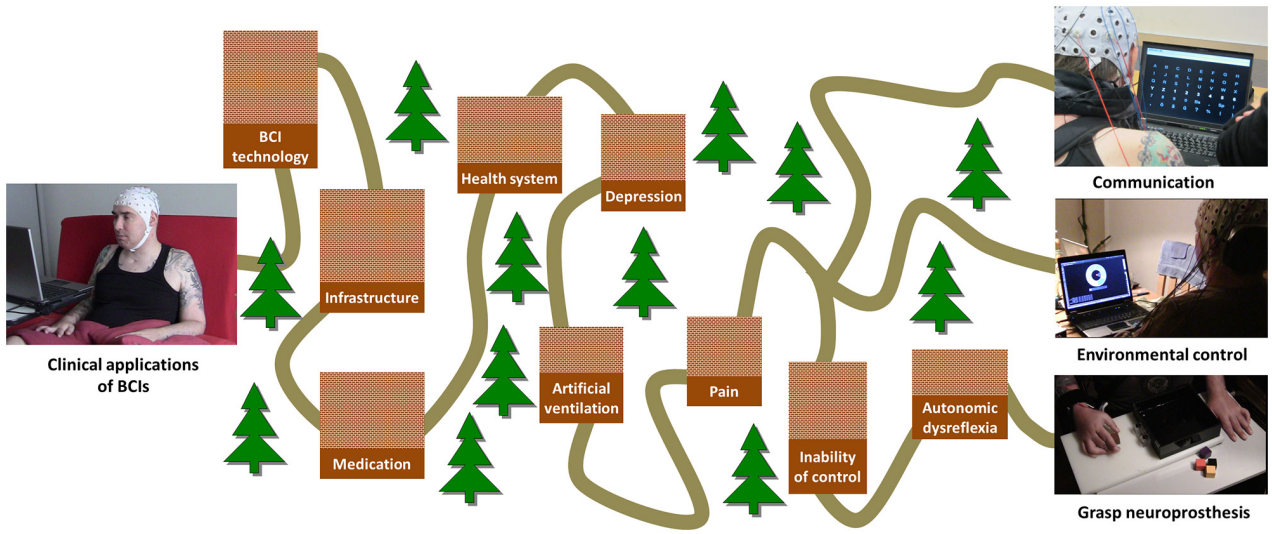

FIGURE 1 | Overview of factors limiting the successful use of different clinical BCI applications. The "long and winding road" of clinical applications of BCI. The height of each barrier encodes its priority.

on the caregivers and the patient. Therefore, a substantial effort needs to be taken to improve the practical applicability of BCIs in clinical routine. This is related in particular to the availability of dry electrodes, which can be quickly mounted and adapted to the individual needs of a patient. Although the first technical implementations of dry or at least "one drop," gel-less electrodes were introduced recently, it needs to be shown that they achieve the same level of signal acquisition quality in particular in an electrically noisy environment and that they do not cause any discomfort to the user (Grozea et al., 2011; Zander et al., 2011; Guger et al., 2012b).

For most effective use of time and personal resources, the necessary action of the therapist should be limited to turning the system on and off. Efforts toward this goal have recently started by implementation of a "push-button" user interface without the need for technical experts to setup and calibrate the BCI system manually (Kaufmann et al., 2012). Further improvements in terms of a higher reliability can be expected from machine learning research in BCIs, as e.g., the transfer of classifiers between individuals bears the chance to circumvent the time-consuming calibration recordings for novel users (Fazli et al., 2009), and novel algorithmic counter-measures have recently been published to adaptively cope with the non-stationarity omnipresent in brain signals (Sannelli et al., 2011; Kindermans et al., 2012; Samek et al., 2012).

MEDICAL AND PERSONAL USER-RELATED FACTORS

Personal factors

During the last decade in industrial countries the mean age at the onset of SCI increased significantly from 28.7 years between 1973–1979 to 42.6 years in 2010–2012 with an ongoing trend toward more patients above the age of 65 (National Spinal Cord Injury Statistical Center, 2012). There is some evidence that the spatio-temporal brain activation patterns alter during aging and that the aging process appears to more substantively alter thalamocortical interactions leading to an increase in cortical inefficiency (Roland et al., 2011). Although, no studies exist that quantify the impact of these cortical changes on the BCI performance, it can be assumed that general cognitive problems of the older population such as attention and concentration deficits might negatively influence the ability to control or to learn how to operate a BCI.

Respiratory problems in high SCI

Particular in patients with high cervical lesions above C4 respiratory problems are present due to the dysfunctions of the voluntary innervation of the diaphragm and/or a thorax trauma. In the acute setting 6.5% of all patients are respirators dependent at least for some hours a day (National Spinal Cord Injury Statistical Center, 2012). 3.5% of the total population have permanent dysfunction of the respiratory function and need artificial ventilation (National Spinal Cord Injury Statistical Center, 2012). These patients are in a real need for a BCI, since other control options might not work satisfactorily. However, electrical artifacts generated by the artificial ventilator or muscular artifacts caused by shoulder elevation for voluntary ventilation support substantially decrease the quality of the EEG signals and might make a successful use of a BCI impossible.

Spasmolytic medication

After the period of a spinal shock spasticity evolves in the muscles in the areas of the body below the level of lesion. This inhibition of reflexes is not only apparent in skeletal muscles, but also in the detrusor muscle of the bladder resulting in episodes of incontinence. The standard medications for treatment of an overactive bladder in the first months after the SCI are anticholinergics that inhibit the receptors for acetylcholine and thereby reducing detrusor muscle tone. It has been shown that anticholinergic effects in the central nervous system can

have negative influence on vigilance and concentration. While the intake of Oxybutynin leads to significant lower spectral power in all relevant frequency bands in the EEG, this effect can be avoided with Tolterodin, Trospiumchlorid, or Darifenacin (Pietzko et al., 1994; Todorova et al., 2001; Kay and Ebinger, 2008). Therefore, a careful selection of the anticholinergic medication for treatment of detrusor muscle overactivity is mandatory to prevent a detrimental effect on the performance of a BCI.

Beside anticholinergics also medication for treatment of spasticity of skeletal muscles such as baclofen, an agonist to GABA-β receptors, have an influence on the EEG spectral power distribution leading to an increase of slow brain waves (Seyfert and Straschill, 1982; Badr et al., 1983). Although systematic examinations on the influence of GABA agonists on the performance of BCI are missing, it can be assumed that the increase of slow waves and decrease of spectral components with higher frequencies will have a negative impact at least on SMR-based BCIs.

In the acute phase patients receive a high dose of medication for suppression of post-operative or trauma related nociceptive pain. A common adverse effect of this medication is its detrimental influence on attention, memory and concentration contributing to tiredness of end users. These effects alter significantly the performance of a BCI (Schreuder et al., 2013).

Autonomic dysreflexia

Autonomic dysreflexia is a potentially dangerous clinical syndrome that develops in individuals with SCI, resulting in acute, uncontrolled hypertension. Briefly, AD develops within the first 6 months after injury in individuals with a neurologic level at or above the sixth thoracic level (T6). AD prevalence rates vary, but the generally accepted rate is 48–90% of all individuals with injuries at T6 and above. Patients with a sensorimotor complete injury have a much higher incidence of AD (91% with complete injury vs. 27% with incomplete injury; Curt et al., 1997). The occurrence of AD increases as the patient evolves out of spinal shock. With the return of sacral reflexes, the possibility of AD increases (Schottler et al., 2009).

Autonomic dysreflexia is caused by the damage of sympathetic spinal fibers and the resulting imbalanced innervation of the autonomous nervous system, which may – if not recognized and treated correctly – lead to long-term complications such as seizures, retinal complications, pulmonary edema, myocardial infarction, or cerebral hemorrhage.

Episodes of AD can be triggered by any painful, irritating, or even strong stimulus below the level of the injury many (Krassioukov et al., 2009). Mainly bladder distension or irritations due to a blocked or kinked catheter or failure of a timely intermittent catheterization program are responsible for 75–85% of the cases (Lindan et al., 1980). AD may also be triggered by electrical stimulation of the lower extremity (Ashley et al., 1993), but has also been seen by the author in very high lesioned patients during the application of a grasp neuroprosthesis.

Although a BCI does not trigger AD, its operation may be negatively influenced by episodes of AD. Additionally, AD may prevent the successful use of a BCI-controlled neuroprosthesis either for therapeutic as well as for compensatory purposes.

Acute stress reaction and episodes of depression after SCI

It is a well-known fact that motivational and emotional states have an influence on the BCI performance of individuals with and without motor impairments independent of the type of BCI used (SMR or P300; Kleih et al., 2010; Nijboer et al., 2010; Hammer et al., 2012). Although, there is nothing predictable about the psychological sequelae after SCI and the response is highly individual and is mediated by both pre-morbid individual characteristics and external factors, several psychological effects occur that might heavily interfere with the successful application of a BCI (North, 1999).

The event of an SCI often occurs within minutes after a trauma or may evolve in non-traumatic causes like ischemia or infections over a few days. The affected persons are not able to slowly adapt to this novel situation, which normally results in an acute stress reaction. Generally speaking, an acute stress reaction is a transient condition that develops in response to a traumatic event. Symptoms occur within 1 month of the extreme stressor and resolves within a 4 week period. They may include a varying mixture of reduced levels of consciousness, withdrawal, anxiety symptoms, narrowing of attention, and disorientation. If the acute stress reaction persists longer than 4 weeks, an adjustment disorder may be present. Adjustment disorders may complicate the course of rehabilitation either by the decrease of compliance with the recommended medical regime resulting in an increased length of hospital stay. Common symptoms of an adjustment disorder include depressed mood, anxiety or worry, feeling unable to cope with life at present or plan ahead, stress-related physical symptoms such as headaches and interference with social functioning or performance of daily activities.

Although, results from systematic investigations on this issue are missing, an acute stress reaction negatively impacts the use of BCIs in patients during the very acute phase up to 4 weeks after the injury.

Additionally to the psychological complication mentioned so far, patients may experience episodes of depression already a few weeks after the injury. Depression is more common in the SCI population compared the general population. Estimated rates of depression among people with SCI range from 11 to 37% (Craig et al., 2014). Common emotional, behavioral, and physical symptoms of major depression are markedly depressed mood, loss of interest, reduced self-esteem and self- confidence, feelings of guilt and worthlessness, reduced energy leading to fatigue, diminished activity, and reduced concentration. All of those symptoms may result in an unwillingness to participate in any kind of rehabilitative training including BCI therapy. Patients suffering from a major depression refuse to be provided with assistive technology in general.

There is also evidence that the P300 amplitude is decreased in individuals with major depression (Diner et al., 1985), which might contribute to the inability to achieve a sufficient level of BCI performance. The inability of BCI control might in turn contribute to an increase in the symptoms of depression. To avoid this vicious

circle a thorough neuropsychological assessment is needed in acute patients to identify any signs of major depression.

SMR-based BCIs and neuropathic pain

Pain is a major problem after SCI and most of the patients report to have pain. In the acute phase after an SCI it is mainly nociceptive pain due to trauma or spams (Finnerup, 2013). Usually within the first year after the injury neuropathic pain develops in about 40–50% of the patients and tends to become chronic (Siddall et al., 2003). Beside the general negative effects of pain on the quality of life of the affected persons, pain leads to deficits in concentration and attention – both having negative impact on the BCI performance. A recent study showed that the EEG activity of spinal cord injured patients with chronic neuropathic pain differs to that of spinal cord injured patients with no pain and also to that of able-bodied people (Vuckovic et al., 2014). Frequency-specific EEG signatures were identified that may be used to monitor the development of neuropathic pain. However, it is not clear if the evolvement of these EEG patterns have a detrimental effect on BCI control.

For operation of an SMR-based BCI users have to imagine movements from different, also paralyzed parts of the body. The influence of MI on neuropathic pain is still an issue of debate and it is not entirely clear, if MI training is lowering or increasing the perceived pain level. It was shown in patients with a chronic thoracic SCI that imagination of foot movements three times a day for a period of 7 days increases neuropathic pain (Gustin et al., 2008). In contrast to this, preliminary studies suggest that neurofeedback has the potential to help patients with otherwise refractory chronic pain (Jensen et al., 2013a). Recent findings indicate that certain EEG activity patterns may be associated with more pain or a vulnerability to experience chronic pain in persons with SCI. Research examining the extent to which changes in this EEG activity may result in pain relief is warranted (Jensen et al., 2013b).

In summary, the use of neurofeedback for prevention of chronic neuropathic pain is still controversial. Clinical studies are urgently needed to reveal if BCIs represent a promising tool to prevent the development of neuropathic pain in SCI.

Inability for BCI control

While BCIs based on the registration of P300 (Guger et al., 2009a) and SSVEPs (Guger et al., 2012a) can be operated by a vast majority of users, it is well-known that SMR-BCIs are not suitable for all users. In up to one third of the non-motor-impaired participants the BCI is unable to detect classifiable task related EEG patterns (Guger et al., 2003). Consequently, these subjects cannot quickly be provided with a BCI-controlled application or need at least a substantial amount of training for sufficient operation of a BCI. The causes for this inability for controlling a BCI (other synonyms are BCI-"inefficiency," BCI-aptitude) have not yet been satisfactorily described. The few studies that explicitly investigated the predictive value of user- and BCI-related factors on BCI performance have been performed with subjects without motor impairments (Kübler et al., 2004; Blankertz et al., 2010; Halder et al., 2011; Holz et al., 2011; Kaufmann et al., 2013). Thus, it is not known, in how far these results are representative also for people with motor impairments such as spinal cord injuries.

In a recent study, a three-class MI screening (left hand, right hand, feet) was performed with a group of 10 able-bodied and 16 tetra- and paraplegic people with a complete SCI with the objective of determining what differences were present between the user groups and how they would impact upon the ability of these user groups to interact with a BCI. Although, the patient group was very heterogeneous in terms of time after trauma and age it is seen that both the tetraplegic and paraplegic patients have some significant differences in event-related desynchronization strengths, exhibit significant increases in synchronization and reach significantly lower mean accuracies (66.1%) than the group of non-impaired subjects (85.1%; Müller-Putz et al., 2014).

In another study, authors compared the BCI performance of 15 end users with complete SCI, eight of them paraplegic and seven tetraplegic (Pfurtscheller et al., 2009). It was found that five of the paraplegic individuals had a mean accuracy above 70% but only one tetraplegic person achieved this performance level. The reason for this observation is still unclear. It can be speculated that the missing sensory loop restricts the vividness of the imagined movements and therefore the performance. This statement is supported by (Alkadhi et al., 2005), who showed the positive correlation of cortical activation and vividness of the imagined movement.

It is a well-accepted statement in the BCI community, that training is expected to improve the performance of SMR-BCIs. Data on the course and performance of long-term MI-BCI training in individuals with chronic high-level SCI is sparse. In one study, two C4, three C6 and four C7 end users were trained to operate an MI-BCI with the goal of controlling a robotic arm (Onose et al., 2012). The average performance of all subjects was quite moderate, determined as 70.5%. In three of the subjects the online performance was up to 20% worse (in a two-class task) than the offline performance. Unfortunately, the authors did not explicitly state how many offline runs were used for classifier training, so it is possible that their classifiers were trained too intensively on the same dataset. This may result in overfitting and therefore suggesting a far higher offline performance than actually achieved during online trials. Furthermore, online experiments are more demanding, which may also affect the performance. One of the study subjects fell asleep during the training, which indicates a high physical and mental workload during the operation of the BCI.

In the framework of a single case study, in which an individual with a lesion of the upper cervical spinal cord was provided with a BCI-controlled upper extremity neuroprosthesis, no training effects occurred over a training time of more than 6 months. Even after 415 MI-BCI runs, the end user's average performance did not show any trend toward improvement, but remained at about 70% with large day-to-day variances. This moderate average performance may be explained by the significant differences in movement-related ß-band modulations found in subjects with SCI as compared to non-injured individuals (Gourab and Schmit, 2010). In detail, a correlation seems to exist between decreased ERS amplitude and the severity of the impairment of the limb

in which the movement was attempted. This supports the view that in high-level tetraplegic subjects, an extensive BCI training period does not necessarily lead to superior results. Although, this statement has to be validated in future studies with a larger population, it must be clearly communicated to patients with an acute SCI. It is entirely possible that only low to moderate performance will be achieved with the danger of causing additional sadness or depression and generating a higher stress level, because severely motor impaired persons may get the impression that in addition to their body even their brains do not work properly.

INFRASTRUCTURE AND HEALTH-CARE SYSTEM RELATED FACTORS

Beside BCI and user-related factors there are factors associated to the typical infrastructure in clinics and to the health-care system in general, which form major barriers for the successful integration of BCIs into clinical routine. Patients rehabilitated in industrial countries take part in normally two sessions of physio- and one session of occupational therapy of a length of 30 min each. With the currently available BCI technology a BCI session takes at least 1 hour to setup the BCI, perform a supervised training/operation and remove the gel from the hair of the patients. Additionally, a BCI needs to be set up and adapted to each individual user, which takes even more time in particular during the first sessions. This means that patients will at least miss two out of three daily sessions of conventional therapy, which is neither accepted by the clinical staff nor by the patients themselves. Therefore, BCIs are likely to be used as adjunct rehabilitative tools with the need for additional personnel or therapy slots. However, these BCI application sessions are not separately reimbursed by the health service or insurances and need to be covered by the budget of the clinics themselves.

The major problem in the field of BCIs is that randomized controlled trials providing clear evidence for their superiority compared to traditional approaches are missing completely (Kübler et al., 2013). In particular, the relationship between the investments in terms of personnel, time and money and the degree of improvement in patient outcomes needs to be determined. This information is mandatory to initiate a dialog with health service payers with the aim of reimbursement of BCI applications during the inpatient rehabilitation phase and later on in the chronic stage also at home.

At this point it must be emphasized that general recommendations on the integration of novel therapies such as the BCI into clinical routine cannot be made due to huge differences in the length of primary rehabilitation between health systems of different countries and in the modes of reimbursement in particular in different European countries.

CONCLUSION AND OUTLOOK

In the context of rehabilitation of individuals with SCI in the acute and subacute stage non-invasive BCIs represent a valuable adjunct to traditional compensatory and restorative approaches in the clinical setting. The main focus of their application is the use as an additional or alternative channel for operation of assistive devices enabling communication and environmental control in patients with very high lesions of the spinal cord. For this application P300-based BCI systems are the first choice, because almost all persons are able to achieve a sufficient level of control with only a small amount of training. MI based BCIs providing a feedback on the modulation of SMRs of the primary motor cortex may evolve to an exciting adjunct to conventional neurorehabilitative therapies aiming at enhancement of motor function by guidance of neural plasticity. This approach is particularly promising, if combined with neuroprotheses of the upper extremity providing a strong proprioceptive feedback. However, clinical studies need to show that no detrimental effects like an increase of neuropathic pain occur during this type of training.

On a more general level, a couple of factors are limiting the successful use of BCIs, among them technology related, user specific and infrastructure dependent factors. The major limitations in the technological domain are the need for gel electrodes with their time-consuming and non-user friendly handling and the need for technical experts for setup and supervision of the BCI. Additionally, user related issues such as spasmolytic and other medication, acute stress syndromes, or episodes of depression may have a negative impact on the BCI performance with the risk of causing additional frustration and sadness. Limited personnel and time resources are a general problem for successful implementation of any kind of novel therapeutic approach in the clinical setting. These may be overcome by regular reimbursement of BCI therapies in the clinical setting. However, to achieve this large scale clinical trials need to be performed, which prove the efficacy and additional benefit of BCIs.

Studies involving individuals with isolated injuries of the spinal cord may provide preliminary information on the feasibility of BCI-based neurorehabilitative approaches in other neurological patient groups like stroke survivors or patients with traumatic brain injury. The challenges and general problems seen in studies with individuals with SCI in the clinical environment are likely to occur also in other patient groups and help to realistically estimate the number of potential end user of BCI technology.

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Effectiveness of the P3-speller in brain–computer interfaces for amyotrophic lateral sclerosis patients: a systematic review and meta-analysis

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A quarter of century ago, Farwell and Donchin (1988) described their mental prosthesis for "talking off the top of your head." This innovative communication system, later named P3-speller, has been the most investigated and tested brain–computer interface (BCI) system, to date. A main goal of the research on P3-spellers was the development of an effective assistive device for patients with severe motor diseases. Among these patients are those affected by amyotrophic lateral sclerosis (ALS). ALS patients have become a target population in P3-speller (and more generally in BCI) research. The P3-speller relies on the visual sensory modality, and it can be controlled by requiring users to actively move their eyes. Unfortunately, eye-movement control is usually not spared in the last stages of ALS, and, then, it is definitively lost in the case of complete paralysis. We reviewed the literature on ALS patients tested by means of P3-speller systems. Our aim was to investigate the evidence available to date of the P3-spellers effectiveness in ALS patients. To address this goal, a meta-analytic approach was adopted. The pooled classification accuracy performance, among retrieved studies, was about 74%. This estimation, however, was affected by significant heterogeneity and inconsistency among studies. This fact makes this percentage estimation (i.e., 74%) unreliable. Nowadays, the conclusion is that the initial hopes posed on P3-speller for ALS patients have not been met yet. In addition, no trials in which the P3-speller has been compared to current assistive technologies for communication (e.g., eye-trackers) are available. In conclusion, further studies are required to obtain a reliable index of P3-speller effectiveness in ALS. Furthermore, comparisons of P3-speller systems with the available assistive technologies are needed to assess the P3-speller usefulness with non-completely paralyzed ALS-patients.

Keywords: brain–computer interface, amyotrophic lateral sclerosis, P3-speller, systematic review, meta-analysis

INTRODUCTION

Twenty-six years ago, Farwell and Donchin (1988) first described a spelling system that exploited event-related potentials (ERPs) for selecting alphanumeric stimuli on a screen, later called the P3-speller. Participants were shown a 6 × 6 matrix of symbols (i.e., letters and functions; **Figure 1**). The rows and the columns of the matrix were randomly flashed, and the participants were required to focus their visuospatial attention on a specific target symbol.

Farwell and Donchin (1988) reported that a rather distinct ERP (i.e., P3 component; for a review about P3, see Polich, 2007) was elicited by the flash occurring in the combination of columns and rows, in which the attended letter was positioned. Moreover, they investigated the possibility to detect the P3 associated with the target letter, by processing offline the ERPs (event-related potentials) through algorithms for signal detection. The first ERP-based brain–computer interface (BCI) was born. Following this seminal study, the P3-speller paradigm has become the most studied one, in the BCI domain (Cecotti, 2011). The success of the P3-speller is mainly due to three reasons. First, it relies on electroencephalography (EEG), which is a non-invasive and cheap technique that can be moved according to the patients' needs (e.g., it can be used at their bedside or it can be implemented on a wheelchair; Daly and Wolpaw, 2008). Second, the P3-speller is an ERP-based BCI, and, thus, it does not require a long training period with respect to BCIs guided by sensorimotor rhythms (SMRs) and slow-cortical potential (SCPs; Birbaumer, 2006). Third, the P3-speller paradigm permits users to select among several symbols/commands. For instance, Townsend et al. (2010) have proposed a 9 × 8 symbols' speller, whereas the SCP- and SMR-based BCIs provide users with fewer choices (the most common is a binary choice; Birbaumer, 2006).

The main goal in BCIs' research is to offer a new channel of communication and control, with particular regard to patients affected by severe motor diseases (Wolpaw et al., 2002). Because of the nature of the illness, ALS patients have been the main target population in BCI studies (for reviews, see Kübler and Birbaumer, 2008; Moghimi et al., 2013). Voluntary muscle control is progressively affected in ALS; thus, in the later stages of the disease the patients become totally paralyzed. The first cause of death in ALS

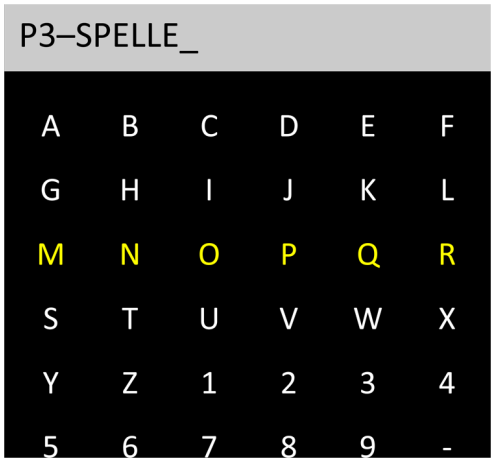

FIGURE 1 | Schematic representation of a P3-speller BCI. Letters and numbers are displayed in a $N \times N$ matrix (6×6 resulting in 36 symbols in the present example). Columns and rows are randomly flashed for a short time (i.e., the third row from the top in this matrix). Users have to focus their spatial attention on the target stimulus (e.g., letters) that they want to select. When the selection is correct, a larger P300 is elicited when the columns and the row containing the to-be-selected target stimulus are flashed. Usually, the classified stimuli are displayed on the top of the matrix.

is respiratory failure (Radunovic et al., 2013). Survival can be prolonged in those of the patients who decide to have respiratory support (i.e., tracheotomy or long-term mechanical ventilation) and the feeding tube (Dreyer et al., 2013). ALS evolves toward the locked-in syndrome (LIS), a condition in which patients remain conscious but they lose their ability to voluntary control most of their muscles (Smith and Delargy, 2005). For instance, ALS-LIS patients may become unable to express their opinions and decisions on important questions regarding their clinical treatment, or their living and biological wills. Hence, effective BCIs could have an enormous impact on the life of ALS-LIS patients, by permitting them to communicate and interact with their environment. Prior to entering the LIS condition, however, ALS patients are still able to communicate, by exploiting their residual motor abilities. Eye-movements are usually one of the last voluntary movements in ALS patients before they reach the complete LIS condition (i.e., CLIS), in which no voluntary muscle control is retained (Murguialday et al., 2011). The reliable control of a muscle (e.g., eye-muscle control) is generally used as a channel for interaction between the patients and their environments. Communication, however, is usually limited to binary yes/no answers to respond to caregivers' and clinicians' questions, whereas the P3-speller offers a higher number of possible choices to ALS patients (i.e., $N \times N$ choices). Then, when reliable control is reached, users do not depend on other people's questions for communicating, but they can spontaneously "speak out" words or sentences. For these reasons, several researchers have proposed the P3-speller as a potential solution for communication problems of ALS patients (Münßinger et al., 2010; Townsend et al., 2010; Manyakov et al., 2011; Li et al., 2011). Unfortunately, the P3-speller is useless for ALS-CLIS patients, because their visual modality is completely impaired (i.e., paralysis of the eyes, dryness of the cornea; Murguialday et al., 2011). Indeed, other sensory modalities must be exploited, with ALS-CLIS patients, in order to develop effective BCIs (e.g., the acoustic modality; Sellers and Donchin, 2006; Kübler et al., 2009). A further limit of the P3-speller is that it requires users to focus their gaze on the to-be-selected target stimulus (e.g., letters, numbers, etc.). In fact, two independent studies on healthy participants have shown that the P3-speller performance relies on the possibility of the users to move their eyes for focusing on the target stimulus (Brunner et al., 2010; Treder and Blankertz, 2010). This represents a further problem with ALS patients, because several oculomotor dysfunctions accompany the progression of the illness (e.g., ophthalmoplegia, defective pursuit eye-movements, saccadic movements' impairment, nystagmus; for a comprehensive review, see Sharma et al., 2011). As a consequence, the P3-speller may be useful only for those ALS-LIS patients who retain sufficient eye-muscle control, and who cannot control communicative prostheses that require limb movements. After focusing on the patients who are in this latter condition, however, there is one main point to be considered. When eye-muscle control in an ALS-LIS patient is sufficient for controlling a P3-speller, it can be reasonably hypothesized that the same patient could control an eye-tracker for augmentative and alternative communication (AAC; Beukelman et al., 2011). Eye-trackers do not need time for electrodes montage and require short calibration time, even with infants (Gredebäck et al., 2009). Furthermore, eye-trackers have accurate, fast and reliable classification performances (Holmqvist et al., 2011), and can be satisfactorily used for hours by ALS patients (e.g., for 300 min; Spataro et al., 2013). Unfortunately, no direct comparison between P3-spellers and eye-tracking spelling systems is available in the literature, to date.

In a recent editorial in which the new horizons of BCI were discussed, Sellers (2013) explicitly formulated the following question: "*Can people with somewhat compromised visual ability benefit from a visual BCI?*" With the present meta-analysis, we aimed to partially address this question (i.e., P3-speller is only one of the available visual BCIs), by focusing on the effectiveness of P3-speller BCIs in ALS patients.

MATERIALS AND METHODS

SEARCH STRATEGIES AND SELECTION CRITERIA

In June 2013 we performed a search on the Pubmed database. We searched the terms "P3-/P300-speller," or "brain-computer interface(s)," or "BCI," or "brain–machines interface(s)," or "BMI," or "man–machines interface(s)," or "direct brain interface(s)," or "mental prosthesis/-es" in combination with each of the following terms: "amyotrophic lateral sclerosis," or "ALS," or "motor neuron disease," or "MND." We searched the reference list of retrieved papers to identify additional relevant articles. Only studies in English were considered for the present systematic review. Original studies reporting P3-speller tests with ALS patients were selected. The choice of a performance's measure that permits a clear and direct comparison across BCIs is a question of theoretical debate in the literature (Dal Seno et al., 2010; Yuan et al., 2013). Thus, for the meta-analysis we avoided the use of information transfer rate (ITR), which is often misreported in literature (Yuan et al., 2013). We identified, instead, the classification accuracy (CA) as our target measure. CA is defined by the percentage of

correct target selection with the P3-speller. CA is a common index of performance reported among BCI studies, and offers a clear idea about BCI systems' effectiveness in target classification. On the contrary, CA does not give any information about the system speed for selecting commands. ALS patients, however, have declared the need of a BCI with CA above 90%, as their priority, followed by the communication speed issue (Huggins et al., 2011). In fact, a fast but unreliable BCI would be useless for paralyzed patients who cannot communicate through other AAC systems.

ENDPOINTS AND STATISTICAL ANALYSIS

For the meta-analysis, we extracted from each study: the CA and its relative measure of variability around the mean (e.g., standard deviation, standard error of the mean, etc.), the year of publication, the chance level (CL = 100/N of matrix symbols) of CA associated to each P3-speller, and the sample size. Each time an ALS patient was tested with more than one P3-speller paradigm, only the best CA was chosen. The CA, defined as the percentage of correct target selection, was used as endpoint for addressing the question of P3-spellers' effectiveness in ALS. The reported measures of variability around the averaged CA of each study (i.e., standard error and standard deviation) were used to compute the 95% confidence intervals around the effect size measure (i.e., the row CA). Because there was a wide variability of experimental designs and of goals among the retrieved studies, there might have been different effect sizes underlying the studies in our meta-analysis. Thus, we calculated the pooled CA by using a random-effects model, assuming that the effect sizes of the studies that actually were performed represented a random sample of the potential real ones (Borenstein et al., 2009; Cumming, 2012). Heterogeneity and inconsistency in the results of the selected studies were assessed by means of Cochran's Q and I^2 tests, respectively (Higgins et al., 2003). To address the possible publication bias (e.g., the fact that studies with non-significant results are less likely to be published), we computed the Kendall's tau rank correlation with continuity correction and the Egger's regression tests (Rothstein et al., 2005). Analyses were performed using Comprehensive Meta-Analysis (v. 2.2.064) and the "metafor" package (Viechtbauer, 2010) of the R statistic software (v. 3.0.1).

RESULTS

The systematic search resulted in 454 non-duplicated records. Of these, 440 articles were excluded because P3-spellers were not tested with ALS patients. Four studies described only single cases of ALS patients (Escolano et al., 2010; Sellers et al., 2010; Aloise et al., 2011; Manyakov et al., 2011), and, thus, they could not be included in the meta-analysis. The averaged CA of the four single cases tested with P3-spellers was 71.82%. Finally, ten eligible studies were identified and were entered in the random-effects model analysis (**Figure 2**).

The estimated CA of these pooled studies was 73.72% (95% CI, 62.55 to 84.89). The estimation of this result, however, is limited by the significant heterogeneity and inconsistency among the considered studies ($Q = 399.41$, $p < 0.001$; $I^2 = 95.71$). Then, a meta-regression on all eligible studies was performed, in which the publication's year was used as moderator. The CA did not significantly increase as a function of time (i.e., publication year; $B = 6.67$, C.I. 95%: −18.8 to 32.13; $Q_{\text{model}} = 0.26$, $p = 0.61$). The funnel plot for publication bias resulted symmetrical to visual inspection (**Figure 3**). The statistical analyses performed for testing the publication bias were both non-significant [Egger's test, $t(8) = 0.822$, p(2-tailed) = 0.43; Kendall's $\tau = -0.35$, p(2-tailed) = 0.15].

DISCUSSION

In the present meta-analysis we investigated the available evidence of the effective use of P3-speller BCIs with ALS patients. The pooled CA of P3-speller with ALS patients was about 74%. This estimated result was affected, however, by huge inconsistency among the analyzed studies. This significant heterogeneity is probably due to differences in study designs (e.g., differences in: sample sizes, number of sessions, classification methods, etc.). Hence, the observed wide variability limits the possibility of safely considering the overall estimation.

Even by assuming that the estimation of the present meta-analysis is correct, some further considerations are necessary. It is clear that a 74% level of CA is far above the chance level (usually lower than 3% with P3-spellers). But, at the same time, 74% is considerably lower than the 90% CA desired by ALS patients (Huggins et al., 2011). Whether a 74% level of CA could be sufficient for everyday use of the P3-speller, remains an empirical question. Of course a 74% level of CA might be considered as satisfactory for patients with no other means of communication. Note, however, that if ALS patients have no other means of communication, they would be probably unable to perform the eye-movements required for controlling the P3-speller.

In most of the studies included in the present meta-analysis, there was a limited number of experimental sessions (e.g., one or few days of testing), which took place often in non-ecological settings (i.e., not at patients' home, which is the last goal for an assistive technology; Kleih et al., 2011). There is only one peer-reviewed report, in which an ALS-LIS patient reached satisfactory long-term control of a P3-speller (for more than 2 years, and at home), with an accuracy above 80% (Sellers et al., 2010). It could be pointed out that the overall CA computed in the present meta-analysis is biased, and the computation could have underestimated the real performance of ALS patients using the P3-speller. Nonetheless, both the tests that we performed on the publication bias were not significant. It is true that the publication bias tests may be underpowered, as a consequence of the small number of studies retrieved for the analysis. But if a publication bias is present, it is more probable that studies that failed to find successful performance were not published, than vice versa. Cases of unsuccessful P3-speller use would have resulted only in a lower CA estimation.

The usefulness of P3-spellers with ALS patients has to be discussed under the light of a further consideration. The performance estimated in the meta-analysis was obtained from samples of ALS patients with sufficiently spared oculomotor functions; otherwise

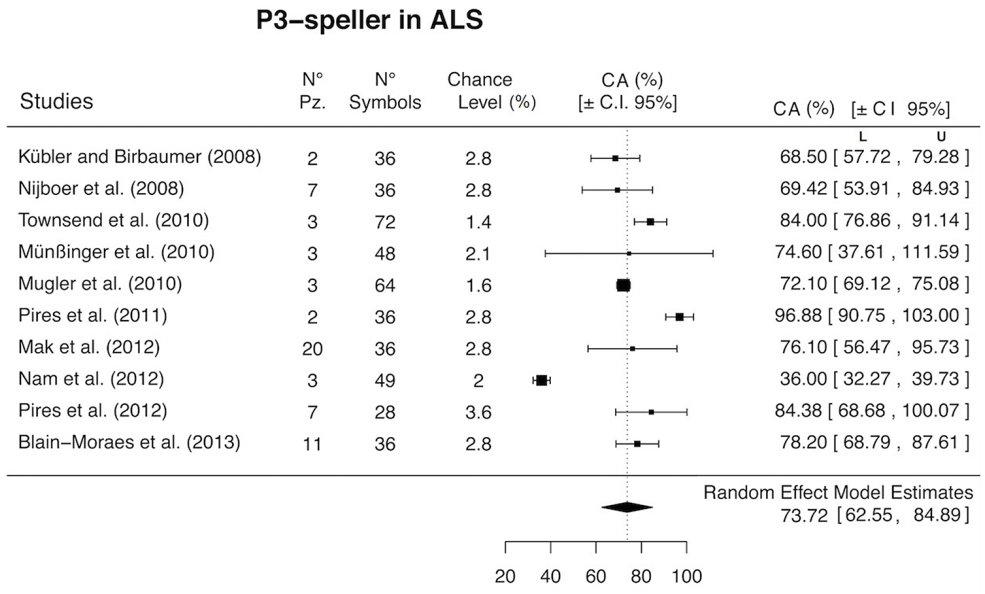

FIGURE 2 | Forest plot of P3-speller accuracy in ALS. The percentage of classification accuracy (CA %) and associated confidence intervals (CIs) are reported for each study. L, lower limit of the confidence interval; U, upper limit of the confidence interval; N° pz, number of patients included in each study; N° symbols, number of symbols displayed in the matrices presented in each study; chance level, the percentage of symbols, in each study, that could have been correctly selected by chance.

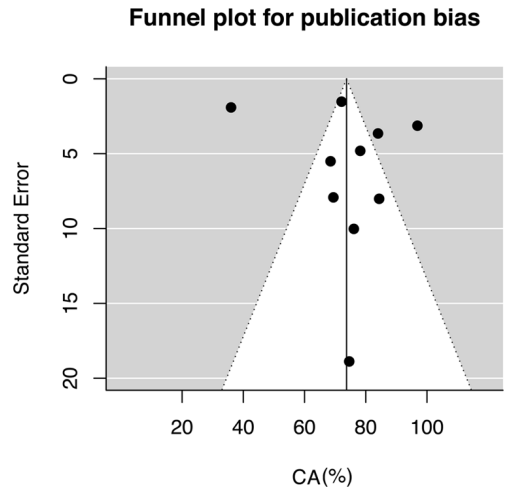

FIGURE 3 | Funnel plot of P3-speller accuracy in ALS. Distribution of studies to the left and to the right of the median line of the funnel plot is rather symmetric, suggesting that there is no evidence of publication bias.

meaningful control of a P3-speller is not possible (Brunner et al., 2010; Treder and Blankertz, 2010). When eye-movement control is spared, a word processor could be controlled even by means of eye-trackers. Pannasch et al. (2008) have described four ALS-LIS patients performing an eye-tracker copy-spelling task, with the possibility of correcting misspelled letters. ALS-LIS patients accomplished the task with 100% accuracy in each tested session, with an average speed of 17 selections per minute. The eye-tracker technique does not require montage of sensors on the user, and it requires only few minutes of calibration for being ready-to-use. Moreover, Spataro et al. (2013) have described a group of 30 ALS patients who satisfactorily used an eye-tracker device for about six hours per day, mainly for communicating with their care-givers. Before thinking to move the P3-speller from the labs to ALS patients' houses, one should consider whether P3-spellers offer any advantage to ALS patients with respect, for example, to the advantages of eye-trackers. To our knowledge, however, there are no peer-reviewed studies in which the ALS patients' performance, in using a P3-speller versus an eye-tracker, has been directly compared.

The findings of the present meta-analysis do not bring clear evidence of P3-speller usefulness with ALS patients. New studies, with larger samples of ALS participants -for increasing power-, with better specified inclusion/exclusion criteria, with detailed assessment of residual eye-movement control, and with clearly and comprehensively reported descriptive statistics are required in order to reach a reliable estimation of P3-speller effectiveness. We would like to underline that our findings are limited to the P3-speller interface, and cannot be in any way generalized to other BCI systems. The eye-movement problem related to the P3-speller is nowadays well known (Brunner et al., 2010; Treder and Blankertz, 2010). Some alternative visual BCIs guided by evoked potentials, and relying on covert spatial attention orienting (i.e., no eye-movement required), have been tested with ALS patients (Lim et al., 2013; Marchetti et al., 2013). Nonetheless, when the visual modality is no more exploitable for ALS-patients, the chances of communication by means of a BCI are entrusted on other sensory modalities (e.g., acoustic or tactile) or on EEG signals other than ERPs (for a review on eye-gaze independent EEG-based BCIs, see Riccio et al., 2012). Despite the huge interest

that the P3-speller has received, and on the basis of the evidence from the present meta-analysis, the early hypothesized goal of translating P3-spellers into a mental prosthesis for everyday use (Farwell and Donchin, 1988), for ALS patients, has not been met yet.

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Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke

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The objective of this study was to investigate the efficacy of an Electroencephalography (EEG)-based Motor Imagery (MI) Brain-Computer Interface (BCI) coupled with a Haptic Knob (HK) robot for arm rehabilitation in stroke patients. In this three-arm, single-blind, randomized controlled trial; 21 chronic hemiplegic stroke patients (Fugl-Meyer Motor Assessment (FMMA) score 10–50), recruited after pre-screening for MI BCI ability, were randomly allocated to BCI-HK, HK or Standard Arm Therapy (SAT) groups. All groups received 18 sessions of intervention over 6 weeks, 3 sessions per week, 90 min per session. The BCI-HK group received 1 h of BCI coupled with HK intervention, and the HK group received 1 h of HK intervention per session. Both BCI-HK and HK groups received 120 trials of robot-assisted hand grasping and knob manipulation followed by 30 min of therapist-assisted arm mobilization. The SAT group received 1.5 h of therapist-assisted arm mobilization and forearm pronation-supination movements incorporating wrist control and grasp-release functions. In all, 14 males, 7 females, mean age 54.2 years, mean stroke duration 385.1 days, with baseline FMMA score 27.0 were recruited. The primary outcome measure was upper extremity FMMA scores measured mid-intervention at week 3, end-intervention at week 6, and follow-up at weeks 12 and 24. Seven, 8 and 7 subjects underwent BCI-HK, HK and SAT interventions respectively. FMMA score improved in all groups, but no intergroup differences were found at any time points. Significantly larger motor gains were observed in the BCI-HK group compared to the SAT group at weeks 3, 12, and 24, but motor gains in the HK group did not differ from the SAT group at any time point. In conclusion, BCI-HK is effective, safe, and may have the potential for enhancing motor recovery in chronic stroke when combined with therapist-assisted arm mobilization.

Keywords: electroencephalography, motor imagery, brain-computer interface, stroke rehabilitation, robotic

INTRODUCTION

Stroke is the third leading cause of severe disabilities worldwide (Hankey, 2013). Despite multimodality rehabilitation efforts, 40% of stroke survivors live with various disabilities. Of these, the lack of functional arm, wrist, or hand recovery contributed to significant losses in independence vocation and quality of life. Task specific technique such as constrained-induced movement therapy (CIMT) is highly effective in reducing learned non-use and improving arm and hand function with enduring gains in chronic stroke. However, only ∼20 to 25% of stroke patients meet minimum criteria for CIMT (Fritz et al., 2005). Since physical practice (PP) of the stroke-impaired extremity is often difficult or not possible using CIMT; motor imagery (MI), the mental practice of movements without physical execution, represents an alternate rehabilitation approach (Sharma et al., 2009). Although MI in chronic stroke is promising, integrating MI in rehabilitation had yielded inconclusive clinical outcome (Braun et al., 2006; Ietswaart et al., 2011; Malouin et al., 2013).

One of the key issues for integrating MI in rehabilitation is that while PP is observable, MI is a concealed mental process. Nevertheless, brain-computer interfaces (BCIs) (Wolpaw et al., 2002) that acquire, analyze and translate brain signals into control commands of output devices (Shih et al., 2012) can be used to detect event-related desynchronization or synchronization (ERD/ERS) (Pfurtscheller and Lopes Da Silva, 1999) when MI is performed. In this way, stroke patients who suffer from severe limb weakness but who are still able to imagine movements of the paretic hand can receive BCI contingent feedback upon detection of MI-related brain signals (Birbaumer et al., 2008; Buch et al., 2008; Ramos-Murguialday et al., 2013). By re-establishing contingency between cortical activity related to MI and feedback, BCI might strengthen the sensorimotor loop and foster neuroplasticity that facilitates motor recovery (Dobkin, 2007; Dimyan and Cohen, 2011). A recent clinical study had shown that Electroencephalography (EEG)-based MI-BCI can be used to detect cortical activity related to MI in a majority of

stroke patients (Ang et al., 2011). Hence the use of EEG-based MI-BCI presents a prospective approach for detecting MI for stroke rehabilitation.

There were many studies that reported the use of BCI for stroke rehabilitation (Ang and Guan, 2013). Recent trials that reported clinical efficacy included: Mihara et al. (2013) reported a randomized control trial (RCT) performed on 10 stroke patients who received near-infrared spectroscopy (NIRS)-based MI-BCI with visual feedback vs. 10 stroke patients who received NIRS-based MI-BCI with irrelevant feedback. The results showed that the patients who received MI-BCI visual feedback attained significantly greater motor improvements measured using Fugl-Meyer motor assessment (FMMA) (Fugl-Meyer et al., 1975) compared to the sham group. The FMMA is a well-designed, feasible, and efficient clinical examination method that has been widely used in the stroke population for measuring sensorimotor stroke recovery (Gladstone et al., 2002). The motor score ranges from 0 for hemiplegia to a maximum of 100 points for normal motor performance, divided into 66 points for the upper extremity and 34 points for the lower extremity. Ramos-Murguialday et al. (2013) reported a RCT on 16 chronic stroke patients who received MI-BCI with hand and arm orthoses feedback vs. 14 chronic stroke patients who received random orthoses feedback not linked to BCI. Both groups received physiotherapy, and the results showed that the patients who received BCI orthoses feedback attained significantly greater motor improvement in FMMA score. Recently, Ang et al. (2014) reported a RCT on 11 chronic stroke patients who received MI-BCI with MIT MANUS shoulder-elbow robotic feedback vs. 15 chronic stroke patients who received intense movement exercises using the MIT MANUS robot. The results showed the patients who received MI-BCI intervention attained an average of FMMA gains of 4.5, and the patients who received intense robot-assisted movement therapy attained an average of FMMA gains of 6.3. However, no significant differences between the two groups were found.

In a systematic review, Nilsen et al. (2010) attested that MI added to PP was an effective intervention for stroke. However, existing RCTs have demonstrated motor improvements in chronic stroke patients who received MI-BCI intervention, but there is still scanty clinical efficacy to indicate the benefits of performing MI compared to PP or standard arm therapy (SAT) in stroke rehabilitation (Ietswaart et al., 2011). Hence we sought to investigate the clinical benefits of concomitant MI, PP interventions for stroke rehabilitation by integrating MI and PP using an EEG-based MI-BCI coupled with a haptic knob (HK) robot (Lambercy et al., 2007, 2011). We then investigated the hypothesis that this integration could facilitate the beneficial effects of therapist-assisted arm mobilization for stroke patients compared to robot-assisted PP and SAT in current rehabilitation program.

MATERIALS AND METHODS

ETHICS STATEMENT

Ethics Committee approval was obtained from the Institution's Domain Specific Review Board, National Healthcare Group, Singapore. The trial was registered in ClinicalTrials.gov (NCT01287975). Informed consent was obtained prior to study enrollment.

STUDY DESIGN

The randomized controlled trial was conducted over ∼2.5 year period from 1 January 2011 to 31 June 2013 at an outpatient rehabilitation facility, involving subjects who had completed inpatient rehabilitation at the Tan Tock Seng Hospital, Singapore. **Figure 1** shows a flow chart of the trial (refer Supplementary Material for CONSORT checklist).

Inclusion criteria included first-ever clinical stroke confirmed on neuroimaging, ages 21–80 years of age, duration >4 months post stroke, moderate to severe impairment of upper extremity function assessed by FMMA (Fugl-Meyer et al., 1975) score 10–50; motor power assessed by Medical Research Council (MRC) (Compston, 2010) grades >2/5 in shoulder abductors, and >2/5 in the elbow flexors, and 1–3 in wrist dorsiflexors and finger flexors and ability to understand simple instructions.

Subjects were excluded if they had medical instability such as unresolved sepsis; postural hypotension; end stage renal failure terminal illness; severe aphasia, inattention; hemi spatial neglect; severe visual impairment; epilepsy; severe depression; psychiatric disorder; recurrent stroke; skull defects compromising EEG cap fit; severe spasticity assessed [modified Ashworth scale (MAS) (Bohannon and Smith, 1987) >2 in any shoulder, elbow or wrist/finger muscles]; pain assessed by visual analog scale (VAS) (Price et al., 1999) >4/10; fixed joint contractures; skin conditions such as infections or eczema which could be worsened by robotic exoskeletal or EEG cap contact.

EEG DATA ACQUISITION

In this study, EEG data from 27 channels were collected using the Nuamps EEG acquisition hardware[1] with unipolar Ag/AgCl electrodes channels, digitally sampled at 250 Hz with a resolution of 22 bits for voltage ranges of ±130 mV. EEG recordings from all channels were bandpass filtered from 0.05 to 40 Hz by the acquisition hardware.

HAPTIC KNOB ROBOT

The haptic knob (HK) robot is a two-degree-of-freedom robotic hand interface for hand grasping and knob manipulation PP (Lambercy et al., 2007, 2011). The hand interface was designed using two parallelogram structures that supported an exchangeable handle in order to adapt to various hand sizes, finger orientations, and subjects with right or left stroke-impaired hand. The HK robot-assisted hand grasping PP involved finger flexion and extension exercises performed using the linear degree-of-freedom (DOF) of the HK, while the rotational DOF was held in a static position. The HK robot-assisted knob manipulation PP involved wrist pronation or supination, and hand coordination exercises performed using the rotational DOF of the HK, while the linear DOF was held in a static position.

During training with the HK, subjects were seated comfortably in a padded, height adjustable chair with 2-point chest strapping without arm rests to reduce compensatory trunk movements. For

[1]Neuroscan Nuamps EEG Amplifier. Compumedics USA, Compumedics Neuroscan and Compumedics DWL, 6605 West W.T. Harris Blvd, Suite F, Charlotte, NC 28269, USA.

each subject, the stroke-impaired forearm was placed on a padded support and the subject was instructed to grasp the end effector of the HK. The height of the chair was adjusted until a comfortable level, the subject's shoulder abducted at about 40° and the elbow flexed at about 90°. The digits of the subject stroke-impaired hand were then strapped to the HK's end effector with Velcro bands to prevent them from slipping.

Instructions and feedbacks were provided on a computer screen for the progress of the HK robot-assisted PP in a form of a picture manipulation task using a solid frame to represent the current position, and a dotted frame to represent the target position. For the HK robot-assisted hand grasping PP, an outward-pointing arrow was shown to instruct the subject to perform hand opening (**Figure 2A**). Once the target outer limit was reached, an inward-pointing arrow was shown to instruct the subject to perform hand closing (**Figure 2B**). This open-and-close action formed a single trial. Subsequently, a different picture was used for the next trial. For the HK robot-assisted knob manipulation PP, a right-curved arrow was shown to instruct the subject to perform a clockwise wrist rotation (**Figure 2C**). Once the target limit is reached, a left-curved arrow was shown to instruct the subject to perform counter-clockwise wrist rotation (**Figure 2D**). This wrist pronation-and- supination action formed a single trial. Similarly, a different picture was used for the next trial. For both the hand

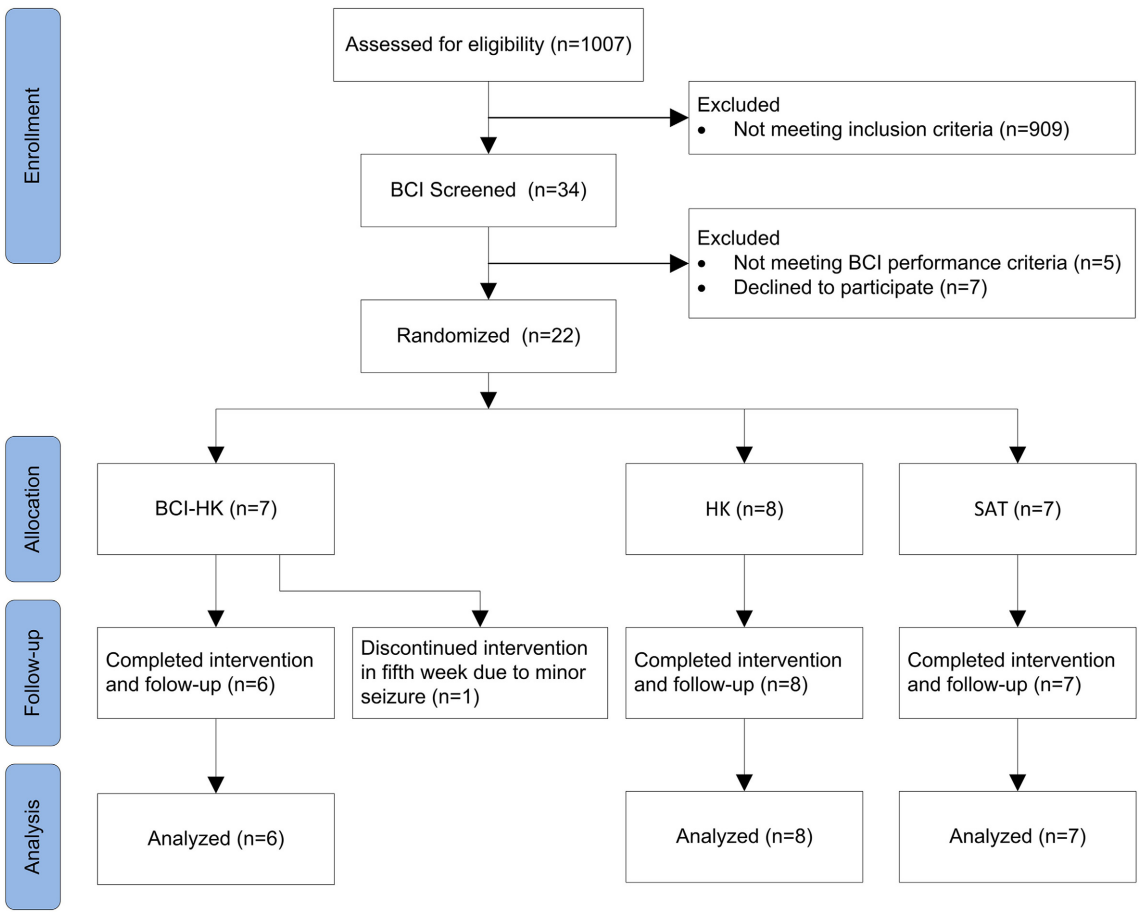

FIGURE 1 | CONSORT Diagram: a flow from recruitment through follow-up and analysis.

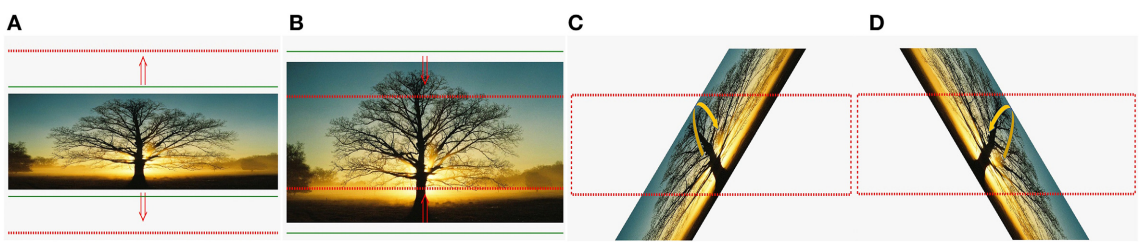

FIGURE 2 | Cues used in BCI-HK and HK interventions. (A) Hand opening; **(B)** hand closing; **(C)** wrist pronation; and **(D)** wrist supination.

grasping and knob manipulation PP, HK robot-assisted movement was initiated if no movement from the subject was detected after an interval of 2 s.

EEG-BASED MI-BCI SCREENING

A study on 99 healthy subjects had shown that ∼7% of the subjects achieved below 60% classification accuracies (Guger et al., 2003). Subsequently, a study on 54 stroke patients had shown that ∼13% of the patients achieved classification accuracies below chance level (Ang et al., 2011). Hence there is a small minority of subjects who cannot operate EEG-based MI-BCI. Thus, in this study, eligible subjects were first screened for their ability to operate EEG-based MI-BCI.

The screening session comprised 4 runs of EEG data collection. The first 2 runs collected EEG from subjects who performed kinesthetic MI (Stinear et al., 2006) of the stroke-impaired hand while strapped to the HK, and idle condition. The subjects were seated comfortably and instructed to imagine moving their stroke-impaired hand in an open-and-close action, and voluntary movements were restrained by static resistance from the HK robot. Subjects were also instructed to minimize voluntary head and body movements. Electromyography (EMG) were recorded from the stroke-impaired hand to check for attempted movements while performing motor imagery (**Figure 3**). In the subsequent 2 runs, the subjects were instructed to relax while passive movement (PM) of the stroke-impaired hand was performed using the HK robot for the hand grasping action. The entire screening session consisted of 4 runs of 80 trials each for a total of 320 trials, and an inter-run break of at least 2 min was provided. Each run comprised 40 trials of MI or PM, and 40 trials of idle condition. **Figure 4A** shows the timing for a single-trial from the screening section. Each trial lasted ∼12 s and each run lasted ∼8 min. The screening session lasted ∼1 h inclusive of EEG setup time. The EEG from the first 2 runs were used to compute the 10×10-fold cross-validation accuracy of classifying MI of the stroke-impaired hand vs. the idle condition using the filter bank common spatial pattern (FBCSP) algorithm (Ang et al., 2012).

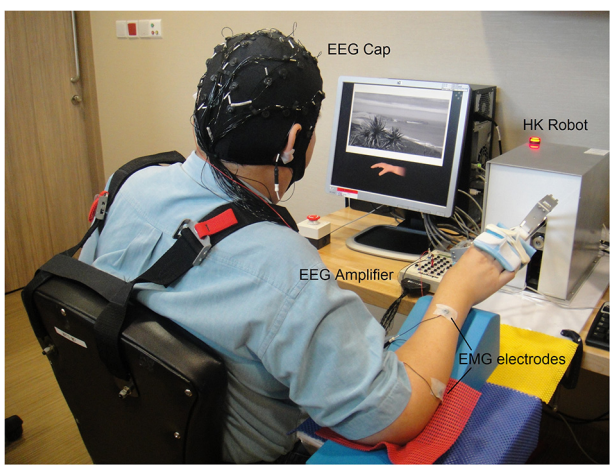

FIGURE 3 | Setup of BCI-HK and HK intervention for stroke rehabilitation at a local hospital. The setup comprised Electroencephalography (EEG) cap, Electromyography (EMG) electrodes, EEG amplifier, and Haptic Knob (HK) robot.

RANDOMIZATION AND BLINDING

Subjects who passed BCI screening were randomly assigned to receive either one of 3 interventions:

(1) BCI-HK which concomitantly comprised EEG-based MI-BCI coupled with HK robot-assisted PP therapy (60 min) followed by therapist-assisted arm mobilization (30 min).
(2) HK which comprised HK robot-assisted PP therapy (60 min) followed by therapist-assisted arm mobilization (30 min).
(3) SAT which comprised distal arm training of forearm pronation-supination movements incorporating wrist control and grasp-release of various objects (60 min) and overall therapist-assisted arm mobilization (30 min) conducted by a trained occupational therapist.

The randomization block size was 3 and the allocation sequence was 1:1:1 generated using STATA software version 10.2 (Stata Corp, College Station, TX, USA). Enrollment and assignment of participants was provided by KSGC. As subject blinding was not feasible, all outcome assessments for this study were performed by occupational therapist DXD who was blinded to allocation. There were no protocol deviations.

All groups received 18 sessions of supervised interventions for a total of 27 h over 6 weeks, 3 times per week, 90 min per session, by occupational therapist GJEJ and engineer KSP. This included 15 min for set up and breaks for short rests. Adverse events via questionnaire were monitored after each intervention session. Discontinuation criteria included new neurological or serious adverse events; increase in arm pain or spasticity of greater than 30% from baseline; or severe fatigue resulted from the interventions.

BCI-HK intervention

The BCI-HK intervention consisted of a calibration session and 18 therapy sessions of MI-BCI coupled with HK robot-assisted PP therapy. **Figure 3** shows the setup for the BCI-HK intervention.

The calibration session comprised 4 runs of EEG data collection that was similar to the screening session whereby subjects performed MI in the first 2 runs and PM in the subsequent 2 runs. The EEG from the first 2 runs were used to compute a subject-specific calibration model using the FBCSP algorithm (Ang et al., 2012) to classify MI vs. the idle condition in the subsequent therapy sessions. The EEG data collected from performing PM were not analyzed in this study.

Each therapy session comprised 4 runs of 30 concomitant MI and PP trials each, for a total of 120 trials. An inter-run break of 3–5 min was provided after each run. Allowable pain-free ranges of motion for the hand grasping and knob manipulation PP were first individually pre-determined by GJEJ. This HK calibration involved calibrating six positions: closing, opening, and static position for hand grasping; clockwise, counter clockwise and static position for knob manipulation. For the first 2 runs, the subjects are instructed to perform kinesthetic MI of the

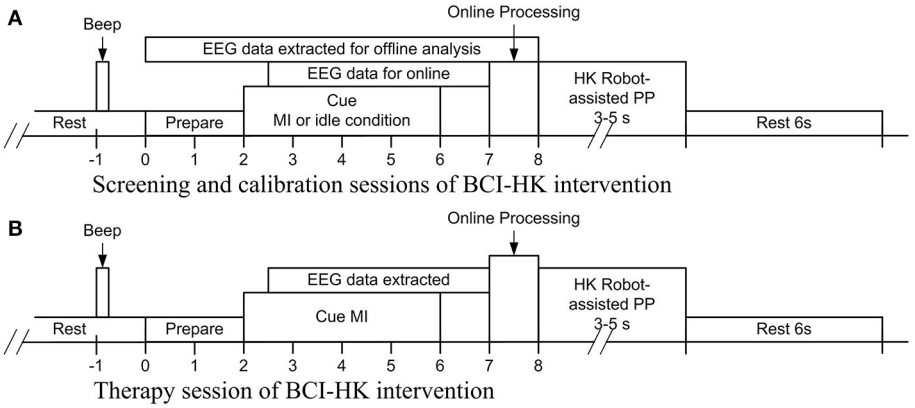

FIGURE 4 | Acquisition of EEG for BCI-HK intervention. (A) Timing of performing kinesthetic MI of the stroke-impaired hand and idle condition for the calibration session; **(B)** timing of performing kinesthetic MI of the stroke-impaired coupled with HK robot-assisted PP for the rehabilitation session.

stroke-impaired hand for the hand grasping action. Subjects were also instructed to minimize voluntary head and body movements. EMG from the stroke-impaired hand was checked to ensure that there was no attempted movement during MI. If MI-related brain signals was successfully detected by the FBCSP algorithm (Ang et al., 2012) using the subject-specific calibration model, then the HK robot-assisted hand grasping PP would be initiated. For the subsequent 2 runs, the subjects are instructed to perform kinesthetic MI of the stroke-impaired hand for the knob manipulation action. If MI was successfully detected, then the HK robot-assisted knob manipulation PP would be initiated. If MI was not detected in 2 consecutive trials, then the HK robot-assisted PP would be automatically initiated. **Figure 4B** shows the timing for a single-trial from the therapy session. Each trial lasted ∼17 to 23 s and each run lasted ∼12 min. Each therapy session lasted ∼1.5 h inclusive of breaks and setup time.

HK intervention

The HK intervention comprised 18 therapy sessions of HK robot-assisted hand grasping, and knob manipulation PP. **Figure 3** shows the setup for the HK intervention, which is the same as the BCI-HK intervention. EEG data was also collected for the HK intervention but was not analyzed in this report.

Each therapy session comprised 4 runs of 30 PP trials each for a total of 120 trials. An inter-run break of 3–5 min was provided after each run. Similar to the BCI-HK intervention, allowable pain-free ranges of motion were pre-determined, and HK calibration was performed by GJEJ prior to the start of the therapy session. For the first 2 runs, the subjects performed HK robot-assisted hand grasping PP. For the subsequent 2 runs, the subjects performed HK robot-assisted knob manipulation PP. If no movements from the subject were detected, the HK would initiate fully assisted PP after 2 s. Each trial lasted ∼9 to 15 s and each run lasted ∼8 min. Each therapy session lasted ∼ 1 h inclusive of breaks and setup time.

SAT intervention

The SAT intervention comprised 18 therapist-assisted sessions. Each session comprised 60 min of repetitive task training (Langhorne et al., 2011) focusing on forearm pronation-supination movements incorporating wrist control and grasp-release of various objects.

Therapist-assisted arm mobilization

All 3 groups received 30 min of therapist-assisted arm mobilization following the principles of the professionally recognized Neuro-developmental Treatment Approach for stroke rehabilitation (Howle, 2002), which included tone management and facilitation toward normal arm movement patterns via various closed-chain functional reach activities.

SAMPLE SIZE STATISTICAL ANALYSIS

The sample size was estimated with an assumption of a 4 point gains in total FMMA score for the BCI-HK and HK groups compared to the SAT group, and a standard deviation of 6.3 points based on the gains of the robot-assisted intervention in the previous study (Ang et al., 2014). The expected number in each group was found to be 20 subjects to achieve statistical power of 80%. Sample size calculation was performed in MATLAB.

STATISTICAL METHODS

Analysis of variance (ANOVA) was used to examine the demographic and baseline group differences. Analysis of covariance (ANCOVA) was used to examine the group differences at each measurement point between the three groups after adjusting for baseline differences. Two-sided t-tests were performed to analyze for significant difference at each measurement point from baseline in each group. One-sided t-tests were then performed to analyze if the BCI-HK and HK interventions were better than the SAT intervention. Data analysis was performed using MATLAB and the level of significance was set at 5%.

OUTCOMES

The primary outcome was the total FMMA score (range, 0–66) for the stroke-impaired upper extremity. Outcomes were measured at 5 time points during the study: at baseline (week 0), at mid-intervention (week 3), at completion of intervention (week 6), 6

weeks follow-up (week 12), and 18 weeks follow-up (week 24). There were no protocol deviations.

RESULTS

PATIENT ENROLLMENT

Thirty-four subjects were found eligible and subsequently screened for their ability to use EEG-based MI BCI. The EEG data collected from the screening session showed 5 subjects achieved accuracies that were lower than chance level (57.5%) and were thus excluded. The chance level performance was computed based on 95% confidence estimate of the accuracy using the inverse of binomial cumulative distribution. Seven subjects declined further participation in the trial. The remaining 22 subjects gave consent and were randomized into 3 intervention groups as follows: BCI-HK (7 subjects), HK (8 subjects) and SAT (7 subjects) respectively. Twenty-one subjects completed the study and follow-up with 1 drop out (4.6%) (**Figure 1**). The study terminated in June 2013 due to funding cessation, thus not all 60 intended subjects could be recruited.

Table 1 shows the demographic of the 21 subjects who completed the study by intervention. Altogether, there were 14 men and 7 women [mean age 54.2 years (30–79)], mean stroke duration, 385.1 days (191–651). BCI-HK group had more subcortical strokes, shorter time after the stroke, and higher FMMA score at week 0. SAT group had higher proportion of cerebral infarctions compared to hemorrhagic strokes. There were no significant baseline differences in all 3 groups in terms of stroke type [$F_{(2,\ 18)} = 0.90$, $p = 0.42$], stroke nature [$F_{(2,\ 18)} = 0.53$, $p = 0.60$], duration since stroke [$F_{(2,\ 18)} = 3.41$, $p = 0.06$], FMMA at week 0 [$F_{(2,\ 18)} = 0.83$, $p = 0.45$], and other demographic.

Table 1 | Demographics and baseline characteristics of subjects by intervention.

Variable	Total	Intervention		
		BCI-HK	HK	SAT
N	21	6	8	7
Age (years)	54.2 ± 12.4	54.0 ± 8.9	51.1 ± 6.3	58.0 ± 19.3
GENDER *N*(%)				
Male	14 (66.7%)	4 (66.7%)	6 (75.0%)	4 (57.1%)
Female	7 (33.3%)	2 (33.3%)	2 (25.0%)	3 (42.9%)
DOMINANT HAND AFFECTED *N*(%)				
Yes	11 (52.4%)	2 (33.3%)	5 (62.5%)	4 (57.1%)
No	10 (47.6%)	4 (66.7%)	3 (37.5%)	3 (42.9%)
STROKE TYPE *N*(%)				
Infarction	11 (52.4%)	2 (33.3%)	4 (50.0%)	5 (71.4%)
Hemorrhage	10 (47.6%)	4 (66.7%)	4 (50.0%)	2 (28.6%)
STROKE NATURE *N*(%)				
Cortical	6 (28.6%)	1 (16.7%)	2 (25.0%)	3 (42.9%)
Subcortical	15 (71.4%)	5 (83.3%)	6 (75.0%)	4 (57.1%)
Duration since stroke (days)	385.1 ± 131.8	285.7 ± 64.0	398.2 ± 150.9	455.4 ± 109.6
FMMA (Week 0)	27.0 ± 13.8	33.0 ± 16.2	25.5 ± 11.5	23.4 ± 14.5

FMMA, Fugl-Meyer Motor Assessment.

EEG SPATIAL PATTERNS AND FEATURES

The EEG from the calibration sessions of patients in the BCI-HK group were used to compute a subject-specific calibration model using the FBCSP algorithm (Ang et al., 2012). **Figure 5A** shows the EEG spatial patterns from patient A006 who performed MI of right stroke-impaired hand vs. the idle condition. The patterns for detecting MI-related brain signals of right hand showed a weak contra-lateral negative region on the left hemisphere and a relatively stronger ipsi-lateral positive region on the right hemisphere around the motor cortex area. The patterns from these two regions corresponded to ERD and ERS respectively for performing right hand motor imagery (Blankertz et al., 2008). **Figure 5B** shows the EEG spatial patterns from patient A031 who performed MI of left hand vs. the idle condition. Similarly, the patterns for detecting MI-related brain signals of left hand showed a weak contra-lateral negative region on the right hemisphere and a relatively stronger ipsi-lateral positive region on the left hemisphere around the motor cortex

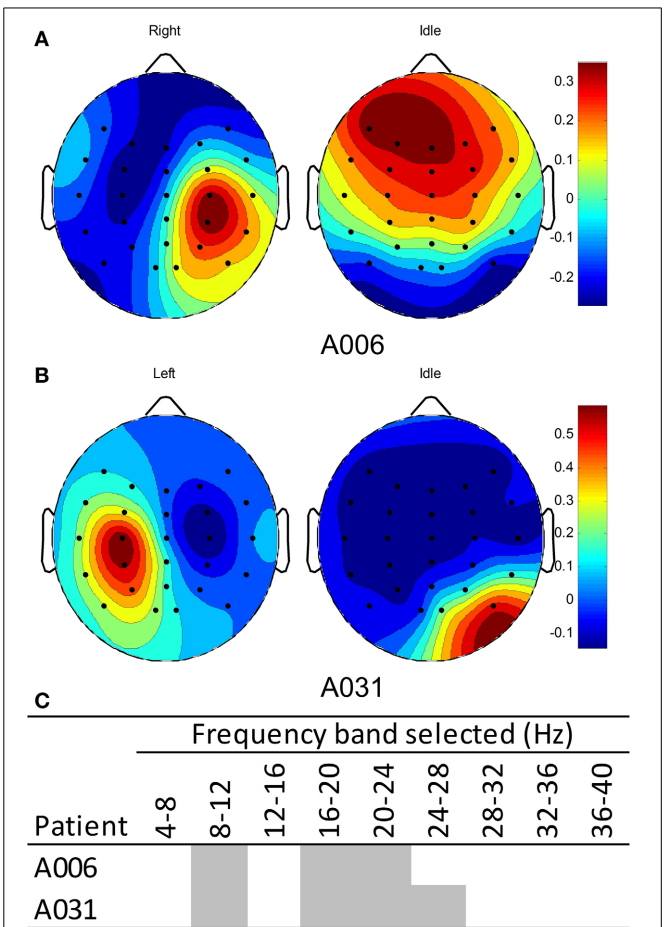

FIGURE 5 | EEG Spatial patterns and frequency bands used to classify motor imagery of stroke-impaired hand vs. idle condition. (A) Spatial patterns of patient A006 with right stroke-impaired hand; **(B)** spatial pattern of patient A031 with left stroke-impaired hand; **(C)** frequency bands used for patients A006 and A031. Blue and red colors in the spatial patterns correspond to negative (ERD) and positive (ERS) values respectively.

area. The patterns from these two regions corresponded to ERD and ERS respectively for performing left hand MI (Blankertz et al., 2008). The weaker stroke-affected contra-lateral regions compared to unaffected ipsi-lateral regions may be due to the relatively lower baseline ERD in stroke patients compared to healthy subjects reported in the study by Kasashima et al. (2012). For both patients, the EEG spatial patterns for the idle condition were not coherent since this condition was not controlled. **Figure 5C** shows the frequency bands selected by the FBCSP algorithm for both patients.

EFFICACY MEASUREMENTS

At week 6, upon completion of interventions, all groups demonstrated significant FMMA score gains compared to baseline FMMA score at week 0: BCI-HK group [$(M = 7.2, SD = 2.3)$, $t_{(5)} = 7.58$, $p = 0.001$], HK group [$(M = 7.3, SD = 4.7)$, $t_{(7)} = 4.35$, $p = 0.003$], and SAT group [$(M = 4.9, SD = 4.1)$, $t_{(6)} = 3.10$, $p = 0.021$]. At weeks 12 and 24, significant FMMA score gains compared to baseline FMMA score at week 0 were sustained for BCI-HK group [$(M = 8.2, SD = 2.9)$, $t_{(5)} = 6.83$, $p = 0.001$; and $(M = 9.7, SD = 2.9)$, $t_{(5)} = 8.04$, $p = 0.001$] and HK group [$(M = 6.5, SD = 4.4)$, $t_{(7)} = 4.14$, $p = 0.004$; and $(M = 8.3, SD = 5.0)$, $t_{(7)} = 4.66$, $p = 0.002$]; but not for SAT group [$(M = 3.6, SD = 5.5)$, $t_{(6)} = 1.71$, $p = 0.14$; and $(M = 3.6, SD = 5.9)$, $t_{(6)} = 1.60$, $p = 0.16$] (**Table 2**).

No significant intergroup differences were observed at any time point during the study among all the 3 groups after adjusting for baseline FMMA score at week 0: week 3 [$F_{(2, 17)} = 1.51$, $p = 0.250$], week 6 [$F_{(2, 17)} = 0.66$, $p = 0.531$], week 12 [$F_{(2, 17)} = 1.12$, $p = 0.349$], and week 24 [$F_{(2, 17)} = 2.39$, $p = 0.122$]. Significant greater upper extremity FMMA score gains were observed in the BCI-HK group compared to the SAT group at week 3 [$t_{(11)} = 2.14$, $p = 0.028$], week 12 [$t_{(11)} = 1.82$, $p = 0.048$], and week 24 [$t_{(11)} = 2.28$, $p = 0.022$]; but not at week 6, [$t_{(11)} = 1.21$, $p = 0.13$] (**Figure 6**). However, no significant greater FMMA score gains were observed in the HK group compared to the SAT group at any time point: week 3 [$t_{(13)} = 1.27$, $p = 0.114$], week 6 [$t_{(13)} = 1.04$, $p = 0.159$], week 12 [$t_{(13)} = 1.14$, $p = 0.138$], and week 24 [$t_{(13)} = 1.66$, $p = 0.060$] (**Figure 6**).

ADVERSE EVENTS

There were no reported serious adverse events, deaths, or significant increases in shoulder or hand pain for any of the 3 intervention groups at any time during the study duration. One subject (4.6%) from the BCI-HK group dropped out in the 5th week of intervention due to a transient mild seizure occurring several hours after the intervention.

DISCUSSION

This is the first RCT that compared 3 arms of MI-BCI, robot-assisted PP and SAT. Difficulties were encountered in recruiting patients for this study due to the strict inclusion and exclusion criteria. In addition, some patients who were clinically eligible did not pass the BCI screening or voluntarily declined to participate due to the length of the study.

The results on the discriminative spatial patterns and frequency band used to classify MI of stroke-impaired hand vs. the

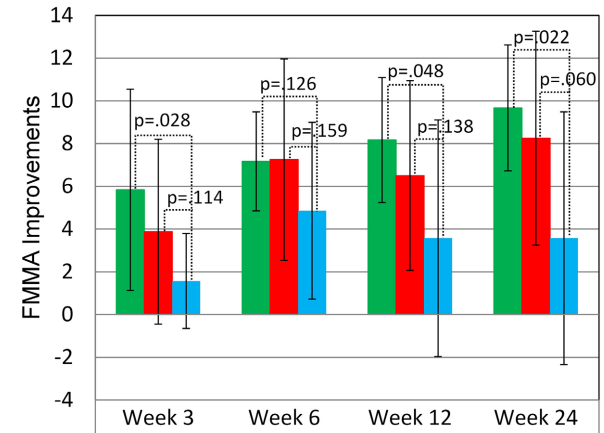

FIGURE 6 | FMMA improvements for BCI-HK, HK and SAT interventions relative to week 0.

Table 2 | Efficacy measures by FMMA scores for each intervention group ($N = 6$ for BCI-HK, $n = 8$ for HK, and $N = 7$ for SAT).

Outcome	Group	Baseline	Improvements relative to week 0			
		Week 0	Week 3	Week 6	Week 12	Week 24
Proximal (0∼42)	BCI-HK	24.2 ± 7.5	3.3 ± 4.2	3.8 ± 2.7	5.0 ± 2.4	5.5 ± 2.1
	HK	19.5 ± 7.7	2.3 ± 2.7	4.4 ± 2.7	4.0 ± 3.5	5.8 ± 2.9
	SAT	18.1 ± 10.4	1.1 ± 2.2	3.0 ± 2.7	2.6 ± 4.4	3.3 ± 4.0
Distal (0∼24)	BCI-HK	8.8 ± 9.2	2.5 ± 2.4	3.3 ± 2.3	3.2 ± 2.7	4.2 ± 3.1
	HK	6.0 ± 4.7	1.6 ± 2.5	2.9 ± 3.0	2.5 ± 2.6	2.5 ± 3.0
	SAT	5.3 ± 4.7	0.4 ± 1.1	1.9 ± 1.9	1.0 ± 1.3	0.3 ± 2.1
Upper Extremity (0∼66)	BCI-HK	33.0 ± 16.2	5.8 ± 4.7	7.2 ± 2.3	8.2 ± 2.9	9.7 ± 2.9
	HK	25.5 ± 11.5	3.9 ± 4.3	7.3 ± 4.7	6.5 ± 4.4	8.3 ± 5.0
	SAT	23.4 ± 14.5	1.6 ± 2.2	4.9 ± 4.1	3.6 ± 5.5	3.6 ± 5.9

idle condition in the BCI-HK group differed from patient-to-patient, demonstrating the necessity to perform subject-specific calibration. The amount of movement repetitions were standardized between the BCI-HK and HK group. However, the number of arm repetitions were not measured in the SAT group, but the duration of training was similar with respect to the other 2 groups. The results showed significant efficacy in reducing both proximal and distal motor impairment, low dropout rate and safety. The results also showed the importance of distal training of the arm for proximal improvement, which is consistent with the study by Lambercy et al. (2011) on 15 chronic patients using the HK robot.

Compared to other chronic stroke patients in robot-assisted PP for proximal and distal (Lo et al., 2010; Lambercy et al., 2011), the FMMA score gains from the BCI-HK and HK groups were higher (∼7 at week 6 vs. ∼3 to 4). Possible reasons included a relatively younger stroke study cohort (mean age 54 years) and larger proportion of cerebral hemorrhages (∼50%) compared to the Caucasian populations who typically have a higher proportion of infarctions.

FMMA score gains at week 6 for all 3 groups were sustained till week 24. Further gains of 2.5 and 1.0 were observed in the BCI-HK and HK groups, and a loss of 1.3 in the SAT group was observed at week 24 relative to week 6. This may be due to the reduction in motor impairment that facilitated further home-based PP.

A significant greater FMMA score gains were observed in the BCI-HK compared to the SAT group. This may be due to the performance of MI in the BCI-HK group that facilitated neuroplasticity, which was suggested from the functional Magnetic Resonance Imaging (fMRI) study on resting state changes in functional connectivity on patients who underwent BCI with robot-assisted rehabilitation after stroke by Varkuti et al. (2013). A greater FMMA score gains were also observed in the HK group compared to the SAT group, but the gains were not significant. This may be due to the highly repetitive and thus higher intensity of PP in the robot-assisted HK group compared to the therapist-assisted SAT group, but lacked the additional positive effects of MI in the BCI-HK group. Similar benefits of MI were seen in another study that investigated chronic stroke patients who received MI-BCI with hand and arm orthoses feedback vs. those who received random orthoses feedback not linked to BCI (Ramos-Murguialday et al., 2013), suggesting a possible role for BCI in rehabilitation for stroke.

STUDY LIMITATIONS

The major limitations of our study were its small sample size and under-powering. This was likely due to the strict criteria required for BCI-related training in terms of cognitive and attention requirements. Due to the small sample size, our results need to be interpreted with caution. Due to a younger and larger proportion of hemorrhagic strokes, which may be expected from a predominantly Chinese population (85.7%), results from our study may lack the ability for generalization as to how the general stroke population will respond to BCI-related rehabilitation. As the number of repetitions was not monitored for the SAT group, there was a lack of standardization on the number of PP trials for this group. In addition, the motor improvements measured by FMMA are limited by a ceiling effect and focused more on proximal arm (Gladstone et al., 2002), thus such gains may not directly translate to changes in activities of daily living.

CONCLUSIONS

There was significant higher motor gain up to 6 months for subjects in the BCI-HK intervention compared with SAT. This adds support to the potential of BCI-HK coupled with rehabilitation therapy as an adjunctive rehabilitation tool for wrist and hand rehabilitation after chronic stroke. Overall side effects were minimal and interventions were well-tolerated. Additional research and larger studies are needed to study neuroplasticity-related changes from the use of BCI in stroke rehabilitation, and to enhance the portability and usability of BCI interfaces.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fneng.2014.00030/abstract

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Brain-computer interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke

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Recent studies have shown that scalp electroencephalogram (EEG) based brain-computer interface (BCI) has a great potential for motor rehabilitation in stroke patients with severe hemiplegia. However, key elements in BCI architecture for functional recovery has yet to be clear. We in this study focused on the type of feedback to the patients, which is given contingently to their motor-related EEG in a BCI context. The efficacy of visual and somatosensory feedbacks was compared by a two-group study with the chronic stroke patients who are suffering with severe motor hemiplegia. Twelve patients were asked an attempt of finger opening in the affected side repeatedly, and the event-related desynchronization (ERD) in EEG of alpha and beta rhythms was monitored over bilateral parietal regions. Six patients were received a simple visual feedback in which the hand open/grasp picture on screen was animated at eye level, following significant ERD. Six patients were received a somatosensory feedback in which the motor-driven orthosis was triggered to extend the paralyzed fingers from 90 to 50°. All the participants received 1-h BCI treatment with 12–20 training days. After the training period, while no changes in clinical scores and electromyographic (EMG) activity were observed in visual feedback group after training, voluntary EMG activity was newly observed in the affected finger extensors in four cases and the clinical score of upper limb function in the affected side was also improved in three participants in somatosensory feedback group. Although the present study was conducted with a limited number of patients, these results imply that BCI training with somatosensory feedback could be more effective for rehabilitation than with visual feedback. This pilot trial positively encouraged further clinical BCI research using a controlled design.

Keywords: brain-computer interface rehabilitation, motor imagery, somatosensory feedback, visual feedback

INTRODUCTION

Stroke leads to a rapid loss of brain function through a disturbance in the blood supply to the brain and usually causes hemiparesis. Data from an earlier study suggest that practicing or observing movements that are highly similar to normal movements helps to improve motor functions (Ertelt et al., 2007; Garrison et al., 2010; Arya et al., 2011). Experience-based plasticity mechanisms, that involve the relative re-weighing of synaptic inputs, are constantly shaping network organization and are more likely driven by the formation and elimination of dendritic spines (Johnston, 2004; Carmichael, 2006; Murphy and Corbett, 2009). Some animal studies suggest that such plasticity occurs at both the peri-lesion and remote areas (Nudo, 2006). The results of several randomized, controlled, trials have indicated that the intensive practice of important motor tasks, while constraining the non-paretic limb, can substantially improve upper limb function in individuals whose movements have been mildly impaired by stroke (Grotta et al., 2004; Mark et al., 2006; Taub et al., 2006; Lin et al., 2010). In the case of moderate impairment, assisted voluntary movement with functional electrical stimulation through surface electrodes is effective in improving finger and wrist motor functions (Peckham et al., 1980; Kimberley et al., 2004).

Recently, electroencephalogram (EEG)-based brain-computer interface (BCI) has been regarded as a new rehabilitation technique for patients with severe impairment after stroke, who cannot use the other above-mentioned rehabilitation strategies owing to a lack of volitional muscle activity (Buch et al., 2008; Daly et al., 2009). Motor imagery is often used in EEG-based BCI, because it is defined as the mental rehearsal of a motor act without overt movement (Alkadhi et al., 2005). BCI estimates the patients' motor imagery from the amplitude of the arc-shaped waveform on an EEG, or a magnetoencephalogram recorded over the primary sensorimotor cortex (SM1) and translates it into feedback (e.g., visual guidance, electrical

stimulation of muscles, or motor-driven orthosis). Imagery, or an actual hand movement, activates the SM1 and rhythmic activity in the alpha and beta band over the hand region results in amplitude attenuation or event-related desynchronization (ERD). This enables movement observation or provides afferent feedback in the BCI, and such feedback is believed to help direct brain reorganization, resulting in some functional recovery from stroke hemiplegia (Daly and Wolpaw, 2008). The prolonged use of this BCI training induces plastic changes in the brain activity of patients with stroke (Rozelle and Budzynski, 1995; Buch et al., 2008) and clinical improvement of upper limb function (Prasad et al., 2009; Caria et al., 2011; Shindo et al., 2011; Ramos-Murguialday et al., 2013; Mukaino et al., 2014)

However, specifications of the BCI paradigm that are needed for functional recovery are as yet unknown. As Daly and Wolpaw speculated, neural plasticity will be guided in different ways depending on the feedback modality. Visual feedback of ongoing SM1 excitability trains patients to produce normal SM1 activity, whereas robotic assistance of paretic movement following SM1 excitation will produce sensory input that induces neural plasticity to restore more normal motor control. To date, different types of feedback have been separately tested in some research groups. Thus, the validation of feedback type and protocol standardization in a BCI rehabilitation context will be beneficial for further research development.

In this paper we compared two different types of feedback (i.e., visual feedback and sensory feedback with robotic movement assistance) contingent to motor-related EEG in stroke patients with chronic hemiplegia with a view toward functional recovery, using the Stroke Impairment Assessment Set (SIAS) which is a known standard scoring test, consisting of 22 subcategories, and has high reliability. BCI settings, except feedback and the task design, were shared between the two paradigms in order to minimize the potential influences of factors such as training intensity, duration, and adaptation to the EEG classification rules. Since such an experiment was first designed as a pilot trial, the experiments were conducted as a group comparison study to minimize participants' burden from an ethical point of view. We note here that data in this BCI paradigm (sensory feedback) was previously reported elsewhere as a preliminary case series study (Shindo et al., 2011). On the other hand, the goal of our study was to compare two different types of feedback. Thus, the same data was used for another research purpose in this article.

METHODS

PARTICIPANTS

The study group consisted of 12 participants who had had a stroke (three with right and nine with left hemiplegia) and met the following inclusion criteria: (1) the first episode was a subcortical stroke; (2) they had severe upper limb paralysis and a score ≤ 2 for finger movement on SIAS (see Appendix) (Chino et al., 1994), indicating very clumsy finger movement and absence of isolated individual finger movement; (3) they had no cognitive impairment; and (4) their chronic stroke injury occurred more than 13 weeks prior to the study to ensure that further neurological and clinical recovery were less likely (Nakayama et al., 1994; Jørgensen et al., 1995; Duncan et al., 2000). Detailed clinical information of the 12 participants is shown in **Table 1**. Twelve participants had little or no detectable surface electromyogram (EMG) activity from the affected extensor digitorum communis (EDC) when they attempted to extend their fingers. All participants provided written informed consent prior to participating in the study.

EXPERIMENTAL PARADIGM

The experimental protocol was conducted in accordance with the Helsinki Declaration and was approved by the ethical committee of Keio University. The experiment consisted of BCI training and brain activity assessment using EEG. The BCI training protocol was similar to that reported previously (Neuper et al., 2009). Participants were seated in a comfortable chair with their arms supported and relaxed on the armrests in pronation. A 15.4-inch computer monitor was placed about 60 cm in front of their eyes. EEG signals were recorded using 10 Ag/AgCl disc electrodes ($\varphi = 10$ mm) placed on both hemispheres (**Figure 1A**). The reference electrode was placed at the left auricle. The signals were amplified (g.USBamp; Guger Technologies, Graz, Austria) and digitized (sampling frequency, 256 Hz). The surface EMG was recorded bilaterally from the EDC muscles (high-pass filter 5 Hz; sampling rate 256 Hz). Impedance of EMG electrodes was kept under 10 kOhm.

EEG signals were processed using MATLAB (MathWorks Inc., USA). Firstly, all bipolar combinations were calculated from five electrodes over each hemisphere. Secondly, all EEG trials were visually controlled for artifacts and contaminated trials were discarded (Neuper et al., 2009). EEG spectra were estimated by fast Fourier transformation, using 1-s window lengths, 90% overlap, and a Hanning window. Feedback was generated on the ERD value calculated for predefined participant-specific frequency

Table 1 | Patient characteristic and clinical evaluation.

Participant	Age	Lesion	TFO (month)	SIAS	Feedback
1	41	Right putamen	4	1a	Visual
2	84	Right caudate nucleus	4	1b	Visual
3	63	Right corona radiate	7	1c	Visual
4	52	Middle cerebral artery area	31	1a	Visual
5	49	Right putamen	13	1a	Visual
6	65	Right putamen	10	0	Visual
7	47	Right thalamus	23	1a	Somatosensory
8	65	Right corona radiate	155	1a	Somatosensory
9	65	Right corona radiate	25	1a	Somatosensory
10	60	Right internal capsule	51	1a	Somatosensory
11	54	Left putamen	23	1a	Somatosensory
12	46	Left putamen	24	1b	Somatosensory

TFO, time from onset.

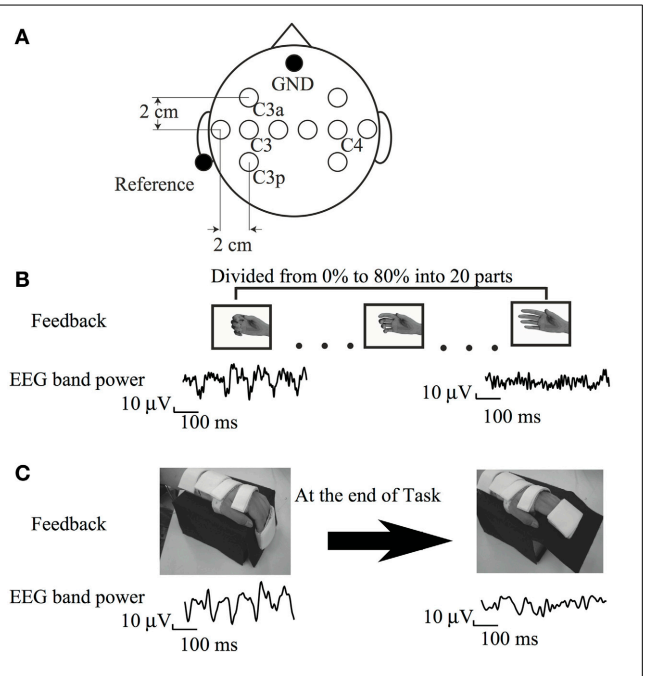

FIGURE 1 | (A) Electrode position **(B)** Visual feedback paradigm **(C)** Somatosensory feedback paradigm cited from Shindo et al. (2011), partially revised.

bands (Pfurtscheller et al., 1997) using the following equation:

$$ERD(f,t) = \frac{R(f) - A(f,t)}{R(f)} \times 100$$

where $A(f,t)$ is the power spectrum of the EEG at frequency f at time t, with reference to the onset of the motor task (see *BCI training* below), and $R(f)$ is the power spectrum of a 1-s epoch of the reference period (2–3 s) in each trial. By using this definition, ERD was expressed as a positive number. The time-frequency map of each bipolar signal was calculated from a 1-s EEG window after every 125 ms. This time-frequency data was used to select the most reactive frequency band and a bipolar montage. If an ERD was not observed at the beginning of BCI training, we used EEG power at a base frequency (9–12 Hz) with a bipolar montage of C3a-C3, which was the best electrode scheme in general (Neuper et al., 2006). A three-factor [time (pre-, post-training), side (damaged, undamaged hemisphere), feedback type (visual, somatosensory)] analysis of variance (ANOVA) for the ERD.

BCI TRAINING SESSION

In this study, there were two feedback groups. Six participants performed BCI training with visual feedback and six participants performed BCI training with somatosensory feedback.

Visual feedback

The trial was initiated upon presentation of the word "Relax" on a monitor, and a countdown was presented at the bottom of the monitor to prepare participants to attempt extension of an affected finger. The word and countdown disappeared 5 s later. Six participants received a visual feedback stimulus from the EEG in the form of a picture of the affected hand on the monitor. The ERD value in response to the resulting action of the feedback was determined before training as follows: firstly, participants generally achieved an increase in sensorimotor rhythm during voluntary relaxation and an ERD while imagining maximal finger extension on the paralyzed side. Pictures of the hand with varying degrees of hand movement were then mapped according to ERD magnitude. We prepared 20 pictures depicting different hand positions, ranging from a full-hand grasp to a fully open hand. A hand opening in the picture was associated with increasing ERD (**Figure 1B**). Pictures of a hand closing were associated with decreasing ERD because the participants' hands were normally positioned in a more grip-like posture during the passive state, caused by spasticity. The ERD was divided into 20 parts from 0 to 80%, and each part was assigned 1 hand picture. The hand picture on the screen then remained stable, and the participants were asked to relax for 5 s. This 15-s trial was repeated for approximately 1 h, and a total of 100 trials were performed. This training was conducted on 5 weekdays for 1 month. The experiment was discontinued for the day if the participant complained of exhaustion. Because some participants complained of exhaustion during multiple sessions, the training time was shortened; however, these participants were asked to perform at least 60 trials on that day.

Sensory feedback

The participants had to imagine the paretic hand opening or at rest for 5 s according to the task cue. The height of the cursor reflected the accumulated value of the output of classification of ERD performed every 30 ms since the beginning of the task. Thus, the cursor fluctuated around the baseline if diminution of ERD was not clearly seen. The cursor went down if the diminution of ERD was continuously observed. The gain of cursor movement was within approximately one-tenth of the vertical range of the monitor during the resting phase in the calibration experiment. From the 4th training day, when the cursor reached the lower half on the right edge of the monitor, the motor-driven orthosis was triggered to extend the paralyzed fingers from 90 to 50° (**Figure 1C**). Each training run consisted of 10 trials, with 5 trials per class, presented in randomized order. Ten training runs were recorded per day, with a total of 100 trials.

Outcome assessment

Surface EMG activities of the affected EDC muscle and ERD were compared between the first and last training days. The task was slightly modified from the BCI training paradigm in order to easily perform paretic finger movements. The cursor moved from the left to right over a period of 8 s on the monitor, and the task cue was presented 5 s after the cursor had appeared. Participants were instructed to perform "unaffected hand opening" or "affected hand opening" voluntarily for 3 s. This training run consisted of 10 trials with 5 trials per class, alternately.

In assessing improvement of finger movement impairment, SIAS was used at pre- and post-BCI training. It consists of a scale from 0 to 5, with 0 indicating complete paralysis and 5 no paresis (see Appendix).

RESULTS

NEUROPHYSIOLOGICAL CHANGES

ERD in most participants was detected over both the damaged and undamaged hemispheres, in alpha and/or beta frequency bands throughout the experiment. **Figure 2** showed the ERD value before/after trainings in both hemispheres. Statistical evaluation of ERD values revealed significant enhancement over both damaged and undamaged hemispheres after BCI training in participants in both feedback categories (ERD values were shown in **Table 2**). Three-Way ANOVA showed no significant differences of side and feedback type, but it became significantly greater over both hemispheres ($p < 0.05$). **Figure 3** shows BCI performance. BCI performance increased in both feedback groups, while there was no significant difference between feedback groups ($p < 0.05$; Two-Way ANOVA).

Figure 4 showed EMG activities of affected EDC before/after trainings. Four participants in the somatosensory feedback group, who had little or no muscle activity before training, showed EMG activity voluntarily, while no participants in the visual feedback group improved their EMG activity. These results indicated that participants in the sensory feedback group improved in finger function and/or voluntary EMG activity. Note here that the visual feedback group did not show any improvement even when they received a longer training period.

CLINICAL BEHAVIORAL CHANGES

Figure 5 showed scores of SIAS finger function test. While no participants in the visual feedback group showed improvement in their finger function, three participants in the sensory feedback group showed improvement in finger function. All participants felt that they could relax more easily, although no participants in the visual feedback group improved on any scores. In addition, participants in the somatosensory feedback group indicated that they became more aware of the use of their paretic upper extremity in daily activities.

DISCUSSION

These results show that EEG-based BCI training with visual or sensory feedback enhanced ERD following attempted motor activity, but only sensory feedback improved motor function. Though only a limited number of patients participated in the current study, the results of this preliminary study suggest that a randomized controlled trial to complement these results be completed in the future.

ERD AND FINGER FUNCTION

Participants in this study learned to increase ERD after training. In addition, BCI performance also increased in both groups. These results follow those of previous studies (Pfurtscheller and Neuper, 2001; Buch et al., 2008; Hwang et al., 2009; Broetz et al., 2010; Hashimoto et al., 2010; Shindo et al., 2011; Cincotti et al., 2012; Mukaino et al., 2014). However, in the visual feedback group, no functional improvement was seen in any participants. From these results, we can say that ERD may not be a direct correlate of functional recovery in finger movement. ERD likely reflects desynchronized neural assembly as a result of the interaction between the thalamic nuclei and cortical areas, that are controlled by the interplay among thalamic relay cells and reticulo-thalamic pathway cells (Steriade and Llinás, 1988; Lopes da Silva, 1991). Desynchronization that is not directly related to motor output is potentially learned by visual feedback BCI.

ERD may reflect SM1 excitability during the relevant motor task (Takemi et al., 2013), thus a proper sensory feedback which engages the participant in the task may facilitate motor reorganization. Moreover, since the nature of neural activity is non-linear, a supplemental neural excitation factor, i.e., timing-dependent cortical excitation by contingent somatosensory feedback to the motor cortex, may promote further excitation of the SM1, resulting in functional recovery. These possibilities could explain why only sensory feedback BCI had a tendency to promote functional recovery in stroke hemiplegia.

Table 2 | ERD values of each hemisphere (mean ± *SD* %).

	Visual		Somatosensory	
	Before	**After**	**Before**	**After**
Undamaged	12.1 ± 8.3	20.0 ± 9.2	15.9 ± 9.7	22.2 ± 11.1
Damaged	13.6 ± 10.4	27.9 ± 5.0	14.1 ± 9.0	26.3 ± 16.9

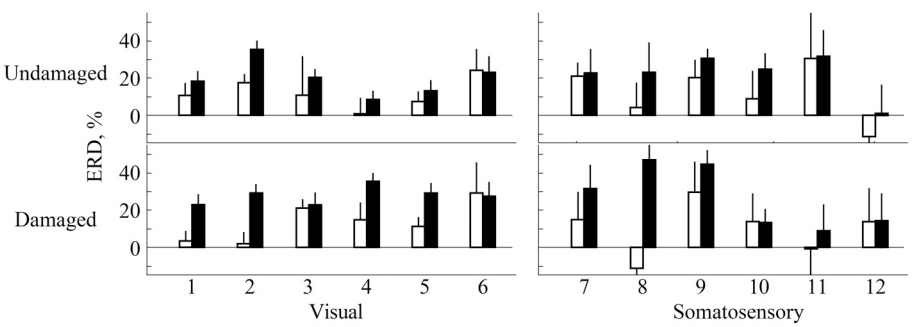

FIGURE 2 | ERD evaluation over both primary sensorimotor areas. White bars represent ERD values before training and black bars represent the ERD values after training. Numbers on x axis represent participant numbers.

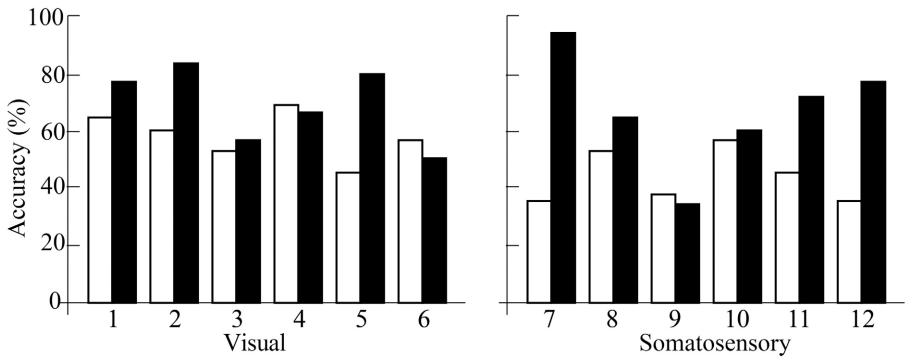

FIGURE 3 | BCI performance accuracy. White bars represent ERD values before training and black bars represent the ERD values after training. Numbers on x axis represent participant numbers.

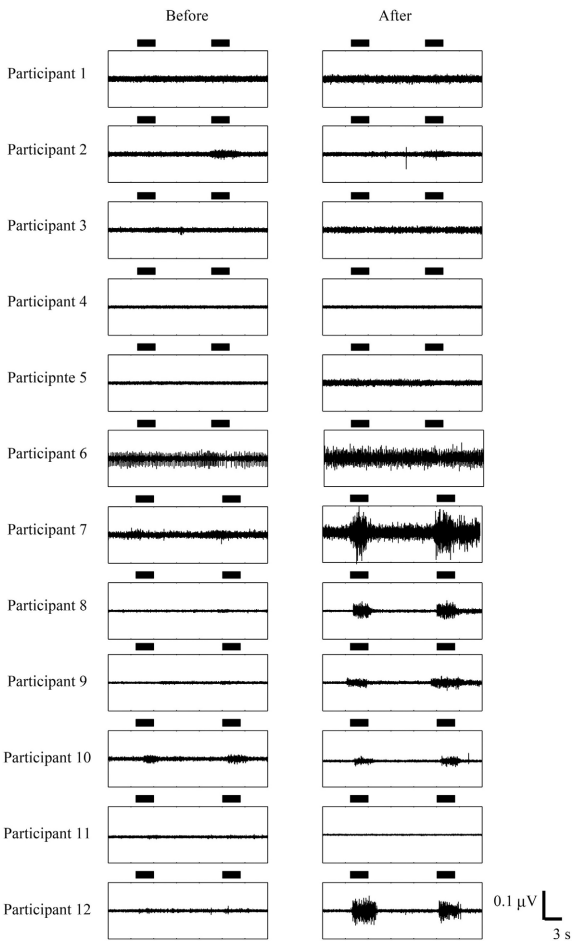

FIGURE 4 | Comparison of EMG activity before and after BCI. The horizontal bars represent the period during which participants opened their paralyzed hands. The data from participant 7 to participant 12 are from Shindo et al. (2011). Permission from Foundation for Rehabilitation Information.

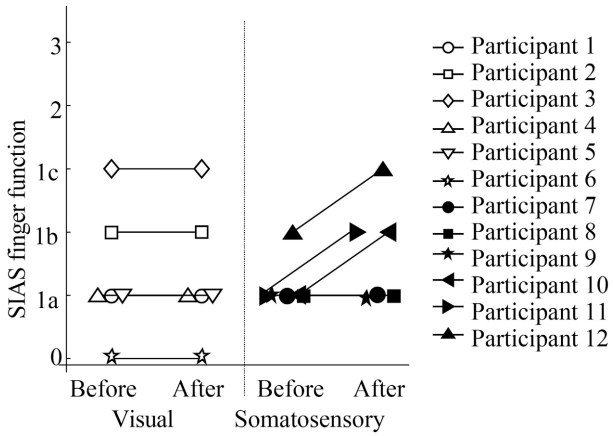

FIGURE 5 | Stroke Impairment Assessment Set (SIAS) finger function scores.

TRAINING INTERVAL

Due to a limitation in hospital regulations, visual feedback training was done on 5 weekdays for 1 month and somatosensory feedback training was done once or twice a week for a period of 4–7 months. Of course, the training schedule should be the same between groups, however the results and remarks remain valid, since even intensive (everyday) and longer (1 month) training with visual feedback BCI did not show functional recovery. This suggests that sensory feedback following a motor attempt may be essential for reorganization of motor function. Intensive bodily sensation of the paralyzed limb may also be helpful to regain body awareness (or ownership), which is needed for motor planning. Such a compound effect may make sensory feedback more advantageous that visual feedback BCI

CONCLUSION

We performed ERD-regulated motor imagery training in a BCI framework in stroke patients who have chronic, severe, hemiplegia, and observed ERD enhancement. Sensory feedback rather than visual feedback of ERD tended to restore paretic finger movement. These results reveal the importance of peripheral bodily sensation contingent to voluntary excitation of the cortical motor system, which is a key in promoting behavioral improvement. This is a serial case study with clinical limitations. Although

the small number of participants, differences in training intervals and duration since stroke are limiting factors, these results provide interesting, positive, data which indicate that a further, large-scale, clinical trial be undertaken, which we expect would support these preliminary insights.

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APPENDIX

STROKE IMPAIRMENT ASSESSMENT SET (SIAS)

Motor Function (Finger)

Finger test: Individual finger movements are tested. The patient flexes each digit from the thumb to the little finger, in that order, and then extends them from the little finger to the thumb.

0: No voluntary finger movement
1a: Minimal voluntary movement or mass flexion
1b: Mass extension
1c: Minimal individual movement
2: Individual movement of each finger is possible, but flexion or extension is not complete
3: Individual movement of each finger is possible with adequate flexion and extension of the digits; however, the patient carries out the task with severe or moderate clumsiness
4: The patient carries out the task with mild clumsiness
5: The patient carries out the task as smoothly as for the unaffected side

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Case report: post-stroke interventional BCI rehabilitation in an individual with preexisting sensorineural disability

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Therapies involving new technologies such as brain-computer interfaces (BCI) are being studied to determine their potential for interventional rehabilitation after acute events such as stroke produce lasting impairments. While studies have examined the use of BCI devices by individuals with disabilities, many such devices are intended to address a specific limitation and have been studied when this limitation or disability is present in isolation. Little is known about the therapeutic potential of these devices for individuals with multiple disabilities with an acquired impairment overlaid on a secondary long-standing disability. We describe a case in which a male patient with congenital deafness suffered a right pontine ischemic stroke, resulting in persistent weakness of his left hand and arm. This patient volunteer completed four baseline assessments beginning at 4 months after stroke onset and subsequently underwent 6 weeks of interventional rehabilitation therapy using a closed-loop neurofeedback BCI device with visual, functional electrical stimulation, and tongue stimulation feedback modalities. Additional assessments were conducted at the midpoint of therapy, upon completion of therapy, and 1 month after completing all BCI therapy. Anatomical and functional MRI scans were obtained at each assessment, along with behavioral measures including the Stroke Impact Scale (SIS) and the Action Research Arm Test (ARAT). Clinically significant improvements in behavioral measures were noted over the course of BCI therapy, with more than 10 point gains in both the ARAT scores and scores for the SIS hand function domain. Neuroimaging during finger tapping of the impaired hand also showed changes in brain activation patterns associated with BCI therapy. This case study demonstrates the potential for individuals who have preexisting disability or possible atypical brain organization to learn to use a BCI system that may confer some rehabilitative benefit.

Keywords: stroke rehabilitation, brain-computer interface, case study, disability, BCI therapy, UE motor rehabilitation, BCI-FES-TDU

INTRODUCTION

Each year approximately 795,000 individuals experience a new stroke in the United States alone (Go et al., 2014), with up to 50% of stroke survivors suffering from some form of persistent neurological impairment (Kelly-Hayes et al., 2003). Brain-computer interface (BCI) technology is being incorporated into an emerging class of devices designed to facilitate the rehabilitation of individuals with persistent motor impairments after stroke (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Liu et al., 2012; Takahashi et al., 2012). These BCI systems detect the user's neural signals, translate these signals into action, and provide real time feedback using various feedback modalities, including visual displays (Prasad et al., 2010), robot-assisted movement (Buch et al., 2008; Broetz et al., 2010; Caria et al., 2011; Ramos-Murguialday et al., 2013; Varkuti et al., 2013), functional electrical stimulation (FES) (Daly et al., 2009; Takahashi et al., 2012), and tongue stimulation (TDU) (Wilson et al., 2012).

Currently, research into the feasibility and efficacy of such BCI devices for applications in stroke rehabilitation focuses largely on individuals whose neurological impairments have been acquired as a direct result of their stroke event. However, there is some

precedent in the feasibility of individuals with disabilities from other etiologies successfully learning to use machine interfaces (Sampaio et al., 2001; Bach-Y-Rita, 2004) and BCI devices. For example, it has been shown that blind individuals can learn to use BCI systems through the use of electrotactile feedback, performing comparably to sighted individuals using visual feedback (Wilson et al., 2012). BCI systems may also be implemented as a means of replacement or augmentative function for individuals who have locked-in syndrome (Kaufmann et al., 2013; Oken et al., 2013; Lugo et al., 2014). However, less is known about the behavioral and neuroimaging changes that may be induced by such BCI systems when used for rehabilitation in individuals with neurological impairments and disabilities prior to stroke.

Approximately 30% of non-institutionalized individuals in the United States over the age of 65 report having a visual, hearing, or cognitive disability (Institute, 2013). Furthermore, 6–13% of individuals in this same age group suffer a stroke each year (Go et al., 2014), resulting in a need for rehabilitative therapies that can be made available to stroke survivors who may have a history of disability prior to stroke. We report the use of a BCI system with coordinated visual, FES, and TDU feedback modalities designed to improve the rehabilitation of upper extremity motor impairment by a subacute stroke subject with a preexisting sensorineural disability (congenital deafness) and a history of depression prior to stroke.

MATERIALS AND METHODS

CASE DESCRIPTION AND PARTICIPANT RECRUITMENT

The participant was a 48-year old male stroke patient whose pre-stroke medical history was significant for deafness due to congenital rubella infection, along with depression and diabetes mellitus. Prior to stroke, the participant had been left-handed with a score of -78 on the Edinburgh Handedness Inventory (Oldfield, 1971) and communicated in ASL using both hands with his left hand as the dominant signing hand. He suffered an ischemic stroke in the right pons (**Figure 1**), which resulted in persistent left-sided hemiparesis. The participant began assessments in this study approximately 4 months after stroke onset. At the time of study enrollment, the participant's medications included sertraline 50 mg daily and metformin 1000 mg daily, which were sufficient to keep his depression and diabetes respectively under control throughout the study period. Other medications included aspirin 325 mg daily, simvastatin 20 mg daily, and Lisinopril 5 mg daily. The subject also received botulinum toxin injections just prior to the beginning of study participation as well as during study participation (**Figure 2**) and took oral baclofen 10 mg three times daily to reduce spasticity. At the time of the study, the participant was able to read and understand written English, although his ability to write with his non-dominant right hand was slow and clumsy. This research was approved by the local Institutional Review Board. The participant provided written informed consent.

THERAPY AND ASSESSMENT SCHEDULE

Neuroimaging and behavioral measures were assessed at three time points prior to the administration of any BCI therapy during a pre-therapy observational period. BCI therapy consisted of 13 2-h interventional therapy sessions using the BCI-FES-TDU system over the course of 6 weeks with no more than three interventional therapy sessions per week.

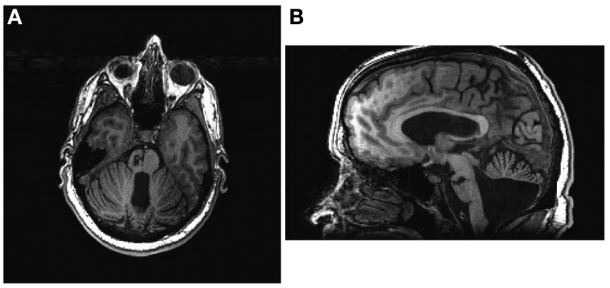

FIGURE 1 | The participant's lesion can be seen in the right pons in both axial (A) and sagittal (B) views. Axial image is presented in radiological conventions.

Behavioral and neuroimaging assessments were then repeated immediately prior to the beginning of BCI therapy, mid-therapy after 3 weeks of intervention sessions, upon the completion of all therapy sessions, and 1 month after the conclusion of all therapy sessions. The subject also received 1–2 h per week of additional occupational therapy and physical therapy during part of the study period administered independently from therapy sessions using the BCI-FES-TDU system. An assessment and treatment timeline for this patient is summarized in **Figure 2**.

BEHAVIORAL OUTCOME MEASURES

Both objective and subjective behavioral measures were assessed at each assessment time point. Objective measures included the Action Research Arm Test (ARAT) (Carroll, 1965; Lyle, 1981; Lang et al., 2006) and grip strength averaged over three attempts as measured by dynamometry. Subjective measures included transformed scores for each subdomain of the Stroke Impact Scale Version 3.0 (SIS) (Duncan et al., 1999; Carod-Artal et al., 2008), the Motor Activity Log (MAL) (Uswatte et al., 2005, 2006), the Wong-Baker pain scale (Garra et al., 2013), and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977; Eaton et al., 2004; Carleton et al., 2013). The Modified Ashworth Scale (Bohannon and Smith, 1987) was also used to measure spasticity in the wrist and fingers of the impaired left side at each assessment.

MRI ACQUISITION AND PROCESSING

All MR images were acquired on a 3 Tesla GE MR750 scanner equipped with high-speed gradients (Sigma GE Healthcare, Milwaukee Wisconsin) using an 8-channel head coil. Padding was used to minimize head movement. Functional scans were run using a T2*-weighted gradient-echo echo planar imaging (EPI) pulse sequence sensitive to BOLD contrast. Technical parameters used to acquire EPI scans were: field of view 224 mm, matrix 64×64, TR 2600 ms, TE 22 ms, flip angle 60°, and 40 axial plane slices of 3.5 mm thickness with 3.5 mm spacing between slices. During each fMRI scan, 70 sequential whole-brain acquisitions were recorded. During EPI scans, the subject was cued to alternate between finger tapping with the left hand and rest

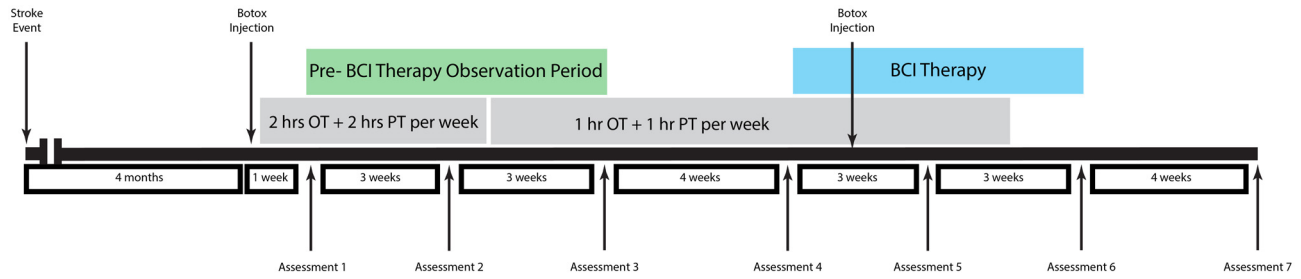

FIGURE 2 | Therapy and assessment schedule.

in blocks of 20 s. In order to cue the participant to alternate between these 20 s blocks, a member of the research team tapped the subject lightly on the arm at the beginning of each 20 s block. This type of cueing was chosen because the participant's vision, while corrected to normal outside of the scanner with glasses, could not be sufficiently corrected within the scanner to allow the participant to read cues projected on a screen. Due to insufficient grip strength and impaired motor control, the subject was unable to use a button box during finger tapping. Instead, the researcher in the scan room who cued the subject also observed the subject's hand to ensure that visible attempted finger tapping or rest occurred as appropriate during each block. Up to three T1-weighted high-resolution anatomical images were also obtained during each scanning session using a BRAVO FSPGR pulse sequence. Technical parameters used to acquire anatomical scans were: field of view 256 mm, matrix 256 × 256, TR 8.16 ms, TE 3.18 ms, flip angle 12°, and 156 axial plane slices of 1 mm thickness with 1 mm spacing between slices.

All pre- and post-processing of MRI data was performed using the AFNI software package (Cox, 1996). The first four volumes of each functional sequence were discarded to allow for signal stabilization. EPI data sets were motion corrected and then spatially smoothed at 6 mm with a full width at half maximum Gaussian kernel. Each voxel timeseries was scaled to a mean of 100, and AFNI's 3dDeconvolve was then used to perform a voxel-wise regression analysis with six motion parameters regressed out. This analysis yielded a voxel-wise t-statistic. EPI data sets were visually inspected for alignment with anatomical T1 datasets, with the best available dataset for each scan session used for alignment. All scan sessions had at least one anatomical T1 dataset with adequate alignment upon visual inspection. Activation maps were then transformed into Talairach space and 3dcalc used to create difference maps across the pre-therapy control and BCI therapy periods. These difference maps were then cluster corrected for multiple comparisons with a minimum cluster size 229 voxels, as calculated using AFNI's 3dClustSim, and thresholded at $t = 2.674$ ($p < 0.01$).

INTERVENTIONAL THERAPY DESCRIPTION

Brain activity was recorded using a 16-channel EEG cap (g.GAMMA cap, Cortech Solutions) and amplifier (Guger Technologies) and processed using BCI2000 software (Schalk et al., 2004) version 2 with in-house modifications to allow for administration of additional tongue stimulation (TDU 01.30, Wicab Inc.) and functional electrical stimulation (LG-7500, LGMedSupply; Arduino 1.0.4).

At the start of each interventional therapy session, the participant was asked to rank how motivated he was to continue participating in this study on a scale of 1–10, with 1 being not motivated and 10 being extremely motivated.

Each session of interventional therapy using the brain-computer interface device then consisted of three stages. The participant first performed open-loop attempted movement of each hand with no performance feedback alternating with periods of rest. Each of these conditions (i.e., attempted movement of the right (or left) hand, or rest) was prompted at least 10 times for 4 s per prompt. The movements used during attempted movement were repeated opening and closing of each hand, which the subject was able to perform although movements using his impaired left hand were noticeably slower and more limited (see **Video S1**).

Attempted movements were used during both the open-loop screening and subsequent closed-loop feedback tasks in order to allow for the mental processes trained during BCI therapy to be as similar as possible to those needed when attempting functional movements beyond the laboratory environment. Motor imagery is a popular means of controlling BCI devices and is found more commonly in the BCI literature than attempted movement. However, this is due largely to the history of the field and is less reflective of an inherent limitation of BCI devices. Many BCI systems were designed with an augmentative purpose in mind, intended to allow for communication in individuals with permanent or progressive motor impairments (Wolpaw et al., 2000). Early BCI systems were also developed using individuals free of motor impairments (Leuthardt et al., 2004) or in individuals whose motor impairments were not targeted by the paradigms used (Wolpaw and McFarland, 2004). In such studies, motor imagery represented a means of establishing control of a device independent of the need for actual movements that a later user with motor impairments relevant to the trained task may not be able to perform. The largely augmentative aims of many BCI devices and the testing of early BCI systems on individuals who were not necessarily affected by the motor impairments that these systems were designed to address contributed to the preferential use of motor imagery as a way to control BCI devices by allowing for early machines to be adapted for the benefit of the largest number of potential users where large variations may exist in the degree of individual motor impairment.

Motor imagery continues to be a good option for the control of a BCI device and has been incorporated into a number of rehabilitative (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Varkuti et al., 2013) and augmentative (Kubler et al., 2005) systems. However, while the goals and populations studied during the development of early BCI devices helped to establish motor imagery as a standard method of control, this precedent does not preclude the use of other mental tasks as potential options for the control of BCI devices (Felton et al., 2007). Furthermore, while the original definition of BCI devices emphasized that these devices could be controlled using motor imagery and mental tasks that do not require the production of actual movement, these definitions did not exclude the possibility that mental tasks accompanied by actual movements could be used for BCI control (Wolpaw et al., 2000). Some newer BCI devices have also begun incorporating attempted movement into their protocols, particularly when the system is intended to serve a rehabilitative purpose (Daly et al., 2009; Prasad et al., 2010; Takahashi et al., 2012; Ramos-Murguialday et al., 2013; Mukaino et al., 2014).

The goal for therapy with the BCI system used in this study was purely rehabilitative rather than augmentative, with stimulus from the BCI device functioning as both a feedback modality as well as a form of assistive support for the production of actual movements in order help to strengthen or reestablish a lost functional capacity. Therefore, actual movements were used to identify appropriate control signals for neural feedback, and the subject was taught to use attempted movements of each hand to control the BCI device. This approach maximizes the similarities between mental tasks trained during BCI therapy and those produced when attempting functional movement in the real world, so that gains made with the device might persist beyond the therapy period. While the device used in this study is controlled by attempted movement rather than imagined movement, we believe that it may still be classified as a BCI system because it allows for neural activity patterns to be detected and translated into a computer-generated feedback response in real time.

Data from open-loop trials was analyzed offline to determine appropriate EEG-based control features for subsequent closed-loop tasks. This initial calibration task and its application to control feedback during later stages of the therapy session is based on previously described processes (Wilson et al., 2009). In summary, the BCI2000 Offline Analysis tool was used to determine the channels for in which the largest r-squared values were found within the frequency ranges for the Mu and Beta rhythms for each condition of attempted movement using either the right or left hand. These channels and the specific frequency bins for which the largest r-squared values were identified were then used as control signals for the closed-loop neurofeedback task. For this participant, control signals were based on the desynchronization of Mu and Beta rhythms detected over the sensorimotor cortex by electrodes placed on the scalp in positions C3, CP3, Cz, C4, and CP4 using the international 10–20 system.

The next stage of the intervention involved a closed-loop condition in which the participant was presented with real time visual feedback to allow him to learn how to modulate cortical activity. Visual feedback was presented in the context of a game in which a target would appear on the left or right side of the screen and the participant was instructed to move a cursor from the center of the screen to the target using attempted hand movement. In this closed-loop condition, attempted movement consisted of either repeated opening and closing of each hand similar to that used for open-loop screening or repeated wrist extension. These actions were used because the participant expressed the desire to improve his ability to open his hand and extend his wrist over other types of movements. The feedback component of this visual display was the lateral movement of the cursor toward or away from the on-screen target, which was controlled in real time by the participant's EEG signals. Attempted hand movements were used to control cursor movement during all trials in this stage as well as in all trials of all subsequent stages. Cortical activity related to attempted movement of the right (left) hand as detected by EEG was translated into rightward (leftward) movement of the on-screen cursor. Each run consisted of 8-12 trials, with each trial randomly presenting one of four possible targets. The participant was given the goal of completing at least 10 runs for this stage as well as during the final stage.

The third stage of the intervention session was similar to the second, using the same game play paradigm with the incorporation of additional feedback in the form of TS and FES to muscles of the impaired left arm to assist with the impaired attempted movement. FES electrodes were applied over the extensor carpi radialus brevis and extensor digitorum muscles in the left forearm to assist with wrist and finger extension. These muscles were chosen for stimulation after the participant reported having more baseline volitional control over active flexion of his wrist and fingers than over wrist and finger extension. TS feedback paralleled visual feedback and provided continuous electrotactile stimulation of the tongue during each trial. Furthermore, TS has been shown to provide sufficient feedback to enable a subject to use a similar BCI device with TS alone in the absence of visual or other tactile feedback (Wilson et al., 2012) and has also been implicated in priming neuromodulation (Wildenberg et al., 2010). TS with this device was organized in a grid that delivers electrical stimulus representing the positions of the on-screen cursor and target onto the tongue. FES was triggered when cortical activity related to attempted movement of the impaired limb was detected by EEG and the participant had been cued to attempt movement of the impaired hand (i.e., when the target was on the left). Thus, since both cursor movement and FES were controlled by the same set of EEG signals, FES was only applied when the cursor moved correctly toward the target on the impaired left side of the body. This triggering of the FES was significant in that it ensured that only consistent, desired patterns of brain activity associated with attempted movement of the impaired left hand were rewarded with feedback from the FES device.

The participant was offered the opportunity to take a short rest break after each stage of the therapy session and was also allowed to take additional short breaks upon request. A picture of game play using all feedback modalities with the BCI-FES-TDU device is provided in **Figure 3**.

RESULTS

CHARACTERIZATION OF BASELINE IMPAIRMENTS

At 4 months after stroke before the administration of any therapy using the brain-computer interface system, the participant had left-sided hemiparesis, which manifested as gait disturbances (the participant walked with assistance of a four-pronged cane) as well as spasticity and weakness in the left shoulder, wrist, elbow, and fingers. At 4 months post-stroke, he signed using his right hand as the dominant hand with little to no use of his left hand while signing, whereas he had been strongly left-handed and used his left hand as his dominant signing hand prior to stroke. A baseline ARAT assessment of each upper extremity revealed a perfect score of 57 with no deficits in the unimpaired right hand in contrast to significant deficits and a total score of 26 for the impaired left hand. The breakdown of these scores by each subdomain of the ARAT is presented in **Table 1**. As can be seen in **Table 1**, the most severely impaired aspects of the participant's upper extremity motor deficit were in the domains of grip and pinch. A baseline measurement of grip strength showed that the subject was unable to produce any measureable grip strength on a standard dynamometer, which is consistent with the significant deficits evidenced in the subject's Grip subscore from the ARAT of his left upper extremity administered on the same day.

FIGURE 3 | Study participant using the BCI-FES-TDU system.

Table 1 | Scores for each subdomain of the ARAT administered at the participant's first visit baseline assessment for the impaired and unimpaired upper extremities.

ARAT subdomain	Score for impaired left UE	Score for unimpaired right UE
Grasp	17	18
Grip	4	12
Pinch	2	18
Gross Movement	3	9

ARAT, Action Research Arm Test; UE, Upper Extremity.

PARTICIPANT COMPLIANCE AND CLINICAL OBSERVATIONS

The participant used the closed-loop neurofeedback BCI device successfully and tolerated the entire course of therapy and assessments without problems, ranking his motivation to continue participating in the study at a 7 or 8 out of 10 throughout the 6 weeks of therapy and answering "No" when asked at the end of all BCI therapy if he had experienced any side effects. It was also noted that, while all ASL communication observed prior to BCI therapy administration used only the participant's right hand, by the end of the BCI therapy period he had begun using his impaired left hand in a limited fashion to assist in the formation of two-handed signs.

BCI RESULTS

The participant was able to learn to use the BCI device, performing with accuracy consistently greater than chance over the course of the therapy period. Cumulative performance accuracy calculated using all completed non-adaptive runs over subsequent sessions is shown in **Figure 4**. An analysis of trials by target location also showed that the subject achieved over 70% accuracy when presented with left-sided targets and over 60% accuracy when presented with right-sided targets when averaged over all sessions.

Although 70% accuracy is sometimes viewed in more traditional studies as a minimum criteria for establishing control of a BCI system, this convention was initially established in the context of a Language Support Program where an accuracy of 70% or more was needed in order to make communication possible (Kubler et al., 2001, 2005). In contrast, the BCI system used in this study was not designed as an augmentative communication system and therefore may not require such a high degree of overall performance accuracy in order to establish BCI control. Furthermore, as game play parameters were dynamically adjusted to make the game more difficult as the participant achieved 70% accuracy at a given level or difficulty, his overall accuracy was

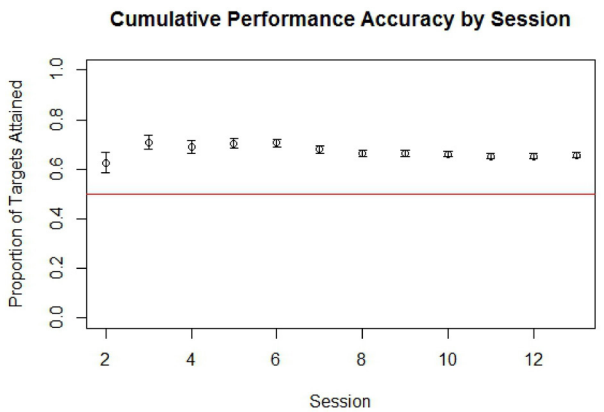

FIGURE 4 | Cumulative performance accuracy in targets attained by run for all completed non-adaptive runs of BCI cursor task game play grouped by session. The red line in is drawn at 0.5, which represents the level at which half of targets presented within a run would be attained by chance. Error bars represent the standard error.

not necessarily expected to be at or above 70%. A binomial also showed the participant's performance accuracy during non-adaptive runs to be significantly better than chance ($p < 0.0001$), indicating that cursor movement was indeed non-random and controlled to some degree by the participant.

BEHAVIORAL MEASURES

The participant showed improvement in both ARAT performance using his impaired left hand and in grip strength of his impaired hand with the administration of BCI therapy. These improvements in ARAT performance with BCI therapy administration were greater than improvements observed during the pre-therapy assessments. Specifically, ARAT scores using the impaired left hand varied from 26 to 32 during the pre-therapy observation period and increased from a score of 27 just before BCI therapy to 40 upon the completion of all therapy and 43 1 month after the cessation of BCI therapy. Similarly, no improvements were appreciated in grip strength measurements until after the completion of BCI therapy, registering an average of 4.33 pounds after the completion of all BCI therapy and 13 pounds 1 month later. The participant's performance on the ARAT and his average measured grip strength using his impaired left hand evaluated at each assessment are summarized in **Figure 5**.

The subjective behavioral measures evaluated at each assessment are shown in **Figure 6**, demonstrating scores for each subdomain of the SIS, and in **Figure 7**, showing results for the each component of the MAL. Subdomain scores for the SIS remained steady or improved over the course of the study period. Some of the greatest gains were observed in the SIS subdomains for hand function and participation, which demonstrated greater gains during and after the period of BCI therapy administration than during initial pre-therapy observation period.

Scores for both the Amount of Use and Quality of Movement aspects of the MAL increased from first measurement during the observational assessment period to the measurement assessed immediately before the beginning of BCI therapy administration. These scores then both continued to increase during the period of BCI therapy administration, peaking at the assessment immediately after the end of BCI therapy. Scores in each of these domains did demonstrate some decline when reassessed 1 month later relative to the assessment immediately after BCI therapy, but even with this observed decline remained higher than scores for all pre-therapy assessments.

Scores on the CES were consistently below 16 points throughout the study period, which is considered to be the threshold for depression using this screening tool (Radloff, 1977; Eaton et al., 2004). Pain scores also decreased during the study period, reaching zero (i.e., no pain) by the pre-therapy assessment and remaining at this level throughout the remainder of the study.

Modified Ashworth Scale scores for spasticity during extension of the wrist and fingers were 0 at all time points. Modified Ashworth Scale scores for wrist flexion and finger flexion are shown in **Figure 8**. Scores were 0 or 1 for wrist flexion throughout the study period and varied from 0 to 2 for finger flexion over the course of study participation.

fMRI RESULTS

Changes were noted in brain activation elicited during finger tapping of the impaired left hand with the administration of BCI therapy. These changes differed from changes observed when no BCI therapy was given. Specifically, a comparison of baseline activation with activation 6 weeks later during a period in which no BCI therapy was administered showed areas of decreased activation throughout the right hemisphere and right cerebellum. In contrast, a comparison of brain activation during the same in-scanner task before and after the period during which BCI therapy

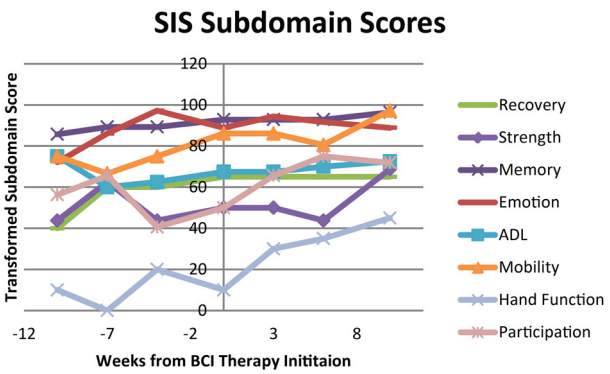

FIGURE 6 | Transformed scores for each of the subdomains on the Stroke Impact Scale (SIS). ADL, Activities of Daily Living.

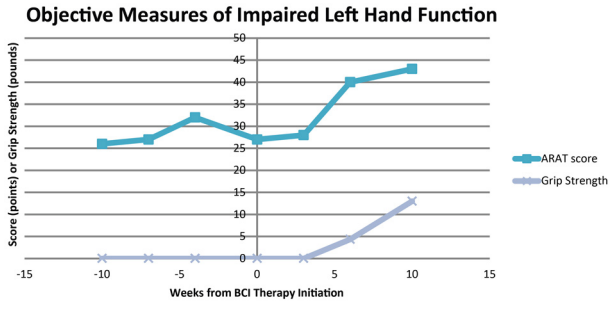

FIGURE 5 | Scores for ARAT performance and average grip strength of the impaired left hand. ARAT, Action Research Arm Test.

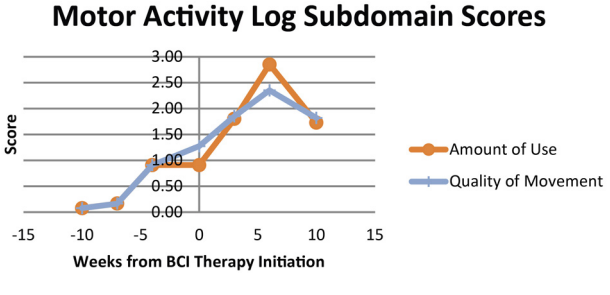

FIGURE 7 | Scores at each assessment for each domain of the motor activity log.

was being administered showed increases in activation throughout the left hemisphere and left cerebellum. These changes are demonstrated in **Figure 9**. Cluster sizes, direction of activation change, and the Talairach coordinates and location for the focus of each significant cluster are provided in **Tables 2**, **3**.

DISCUSSION AND CLINICAL IMPLICATIONS

The results of this study show that it is possible for a stroke survivor with preexisting neurological impairments, in this case sensorineural deafness, to effectively use a BCI device during interventional rehabilitation therapy. The participant's ability to use the BCI device without issue is supported by his consistent performance above chance (**Figure 4**) along with his self report indicating that he experienced no side effects during the therapy period. Furthermore, the participant achieved gains in both objective and subjective behavioral measures during the time period concurrent with the administration of BCI therapy that were greater than any gains observed during the pre-therapy observation period during which no BCI therapy was administered. These functional gains were accompanied by changes in brain activation observed during attempted finger tapping of the impaired hand, which were again observed with the administration of BCI therapy but not during the pre-therapy observation period.

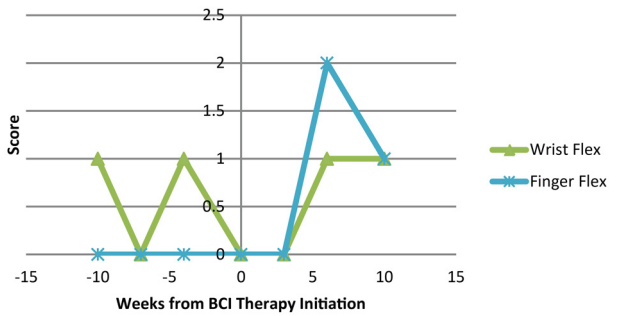

FIGURE 8 | Modified Ashworth Scale scores for flexion of the wrist and fingers at each assessment.

To our knowledge, this is the first reported case of a deaf individual learning to use a BCI device for the purpose of motor rehabilitation. There have been a number of studies examining the feasibility of adapting BCI devices for use by individuals with visual impairments (Guo et al., 2010; Wilson et al., 2012; Lim et al., 2013; McCreadie et al., 2013) and numerous studies on the ability of individuals with conditions such as amyotrophic lateral sclerosis to control BCI devices (Kubler et al., 2005; Bai et al., 2010). However, in the majority of such cases the use of the BCI device is intended to augment or replace an impaired function in an otherwise neurotypical individual rather than to rehabilitate a superimposed neurological impairment. This case study is limited in its ability to generalize the results observed here to other individuals with similar impairments, as it only documents the outcomes achieved by a single participant. However, the fact that this participant was able to learn to use the BCI system and demonstrate gains in behavioral measures shows that

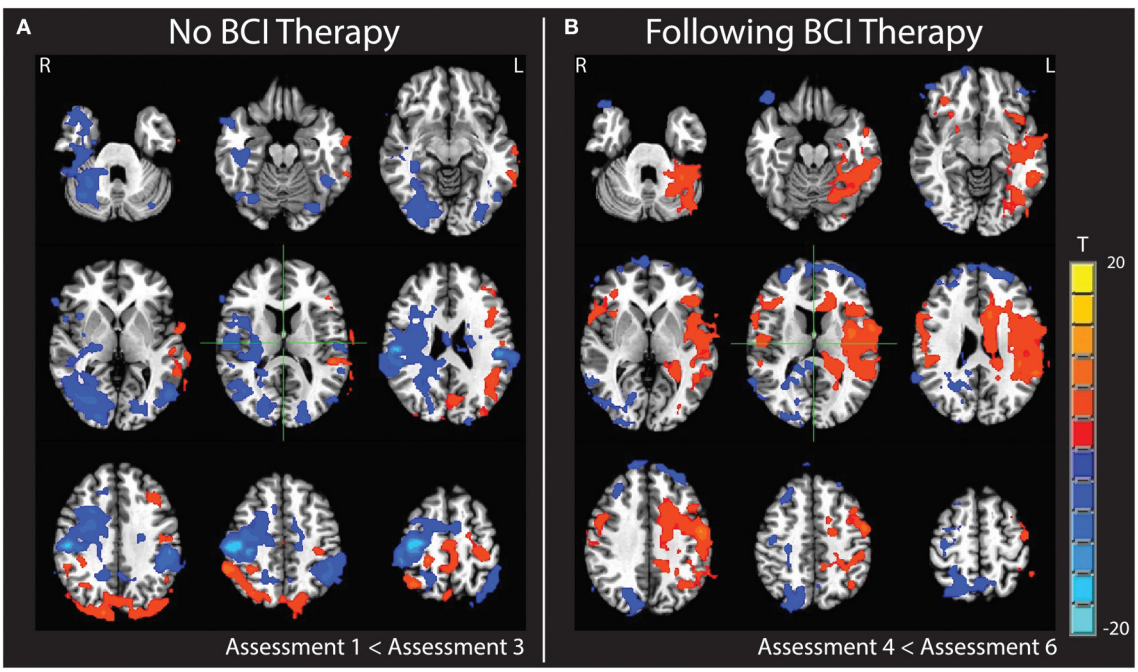

FIGURE 9 | Subtraction maps demonstrating differences in brain activation during finger tapping of the impaired hand. Maps compare activation patterns at week 6 of observational control (assessment 3) minus initial baseline activation (assessment 1) **(A)** and changes observed comparing activation post-therapy (assessment 6) minus pre-therapy (assessment 4) **(B)**.

Table 2 | Changes in brain activation during finger tapping of the impaired left hand from assessment 1 to assessment 3 during which no BCI therapy was administered.

Cluster	X	Y	Z	Region of cluster focus	Size (voxels)	Increase or decrease in activation
1	−49.5	22.5	41.5	Right postcentral gyrus	10,662	Decrease
2	49.5	64.5	2.5	Left inferior temporal gyrus	789	Decrease
3	31.5	31.5	50.5	Left postcentral gyrus	476	Increase
4	46.5	31.5	14.5	Left superior temporal gyrus	378	Increase
5	46.5	40.5	−45.5	Left cerebellum	369	Increase
6	43.5	−19.5	20.5	Left middle frontal gyrus	259	Increase

Coordinates provided are in Talairach space.

Table 3 | Changes in brain activation during finger tapping of the impaired left hand from assessment 4 to assessment 6 during which BCI therapy was administered.

Cluster	X	Y	Z	Region of cluster focus	Size (voxels)	Increase or decrease in activation
1	49.5	7.5	35.5	Left precentral gyrus	6582	Increase
2	−22.5	52.5	56.5	Right superior parietal lobule	2342	Decrease
3	46.5	−43.5	11.5	Left middle frontal gyrus	1093	Decrease
4	−34.5	−34.5	−3.5	Right middle frontal gyrus	923	Increase
5	−43.5	−37.5	−12.5	Right middle frontal gyrus	230	Decrease

Coordinates provided are in Talairach space.

it is clearly possible for at least some individuals with preexisting disabilities or with atypical neurological characteristics prior to stroke to learn to control such devices and to potentially benefit from rehabilitative applications of these of therapies. This result is also consistent with prior work showing that no greater mental workload is incurred by individuals with physical disabilities when using BCI devices compared to healthy neurotypical control subjects performing the same tasks (Felton et al., 2012).

These results are promising both for the field of BCI technologies in stroke rehabilitation as well as for individuals with preexisting disabilities or neurological conditions that may benefit from them. It has been suggested that the minimal clinically important difference in ARAT improvement can range from as few as 6 points for chronic stroke patients (Van Der Lee et al., 2001) to 12 points for acute to subacute stroke patients with impairments of their dominant hand (Lang et al., 2008), and the participant's improvement in ARAT during the period in which BCI therapy was administered exceeded even a 12 point gain. In this case, these improvements in motor function also had a noticeable impact on the participant's ability to communicate, which may be reflected indirectly by his gains in SIS participation and more directly by the clinical observation that when communicating in the presence of the researchers the participant began using his impaired left hand to form ASL signs only after he began receiving BCI therapy.

The subject made notable gains in other measures assessed as well, showing concrete improvements in grip strength upon completion of BCI therapy as well as greater improvements in some subdomains of the SIS during the period during and after BCI therapy than during the pre-therapy observation period. Similarly, scores in each domain of the MAL increased during both the per-therapy observation period as well as during the period of BCI therapy administration, with the most dramatic increase being observed immediately surrounding the period of BCI therapy. However, the decline in scores for this measure at the final assessment in the absence of similar declines in the objective measures and in SIS scores may also reflect larger amounts of variability in MAL scores after the intervention, as the MAL has been shown to be most stable when assessing chronic stroke patients not undergoing an intervention (Van Der Lee et al., 2004), unlike the participant in this study. The improvements in MAL scores may also be reflecting, in part, improvements associated with the outside therapies administered or with study participation and interaction with study personnel, which were at a minimum during the 1 month period between the cessation of BCI therapy and the final assessment.

One major limitation of this study is the inability to clearly separate the effects of the interventional BCI therapy from effects of the additional occupational therapy, physical therapy, and botulinum toxin treatments that the participant received during the study period. Therefore, it is necessary to acknowledge that some or all of the functional gains described above may be attributed to spontaneous recovery, to the standard (i.e., non-BCI) therapies that the participant received during the study period, or to some combination thereof. However, although it is possible that none of the improvements described in this study were induced or facilitated by the BCI therapy, it seems unlikely that BCI therapy made no contribution to the gains observed specifically during the period during which BCI therapy was administered.

It is similarly not possible to determine what relative contributions various components of the BCI therapy, such as the neurofeedback training, the repeated attempted movement, or the FES, may have had to the recovery observed. However, the

participant's BCI performance results suggest that he remained engaged in the neurofeedback task throughout the study period, so the gains documented during the therapy period do appear concurrent with regular neurofeedback training. While this study is unable to differentiate among the rehabilitative effects of interventional BCI therapy components and the effects of outside therapies and spontaneous recovery, it does serve as a demonstration for the potential of BCI therapy to serve as a component of an individualized rehabilitative regimen that may on the whole lead to gains in post-stroke motor recovery for individuals with preexisting disabilities.

It is also worth noting that the subject actually received more physical and occupational therapy during the observational control period of the study than during the period when BCI therapy was being administered and no outside therapies during the final weeks of BCI therapy and post-BCI therapy follow-up. Thus, the improved gains observed during and after BCI therapy occurred during a time period when additional therapies were either reduced or stopped altogether.

With regard to botulinum treatments, some studies have found botulinum toxin to improve upper extremity use and reduce disability in patients with upper extremity spasticity following stroke (Brashear et al., 2002; Pandyan et al., 2002; Rousseaux et al., 2002), but improvements in such studies are often highly variable. Some such gains are based on subjective self-report alone (Brashear et al., 2002), while others document improvements in objective measures of hand function in fewer than half the individuals receiving botulinum toxin treatment (Pandyan et al., 2002). One systematic review of neuromuscular blockade in upper extremity spasticity found that while tone may improve with botulinum toxin treatment, no clear functional improvements could not be convincingly demonstrated in the literature (Van Kuijk et al., 2002). Furthermore, it is important to note that by chance the participant's botulinum toxin schedule was similar between the pre-therapy and BCI therapy periods in that botulinum toxin was administered within 13 days of each baseline assessment (i.e., the first pre-therapy observational assessment and the assessment just before the initiation of BCI therapy). However, the most significant functional gains observed were seen only with BCI therapy administration during a time when spasticity measures either increased or remained similar to pre-therapy levels (**Figure 7**). Together, the similarity in botulinum toxin schedules and the absence of significant reductions in measured spasticity between the observational and BCI therapy periods suggest that the improvements documented with BCI therapy are unlikely to be attributable to the patient's botulinum toxin therapy.

While there is no way to definitively establish the cause of the increase in finger flexor spasticity observed near the end of the therapy period, one possible explanation for this finding is that finger flexors may have been strengthened during therapy when faced with increased resistance posed by the FES of the antagonizing extensor muscles. With the subject attempting repeated opening and closing of the hand and stimulus applied only to the extensor digitorum, repeated attempts to activate finger flexors during or just after extensor stimulation may have resulted in increases in strength and tone of the finger flexors. This increase in strength or tone of finger flexor muscles may also have contributed to the observed increases in the participant's ability to generate measurable grip strength near the end of the therapy period.

While most stroke survivors with motor impairments experience some functional recovery in the acute and subacute stroke periods either spontaneously or with traditional rehabilitative therapies, many reach a functional plateau within the first 6 months to 1 year after stroke and are left with motor impairments that can persist years. It has been suggested that the potential for further recovery remains in stroke survivors who have reached such a plateau and that newer therapies may facilitate this recovery where traditional therapies have ceased to produce measurable gains (Cramer, 2010). BCI therapy is one class of these newer therapies thought to help harness this potential for additional recovery. EEG-based BCI devices, such as the one employed in this study, detect the user's neural activity in the form of EEG signals and use these signals to provide real time feedback. These BCI systems have been coupled with various feedback modalities, including visual (Prasad et al., 2010), robotics (Buch et al., 2008; Broetz et al., 2010; Caria et al., 2011; Ramos-Murguialday et al., 2013; Varkuti et al., 2013), FES (Daly et al., 2009; Takahashi et al., 2012), and TDU (Wilson et al., 2012) by which the user can learn to modulate their brain activity.

In the context of motor rehabilitation therapy, this type of feedback is thought to strengthen central-peripheral connections and promote neuroplastic change by rewarding the production of consistent patterns of brain activation in conjunction with the subject's intent to move. Early studies of stroke survivors using such devices for rehabilitation have been promising, demonstrating functional gains (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Liu et al., 2012; Takahashi et al., 2012) as well as concurrent changes in brain activity and organization (Caria et al., 2011; Ramos-Murguialday et al., 2013; Varkuti et al., 2013). In this study, the changes in brain activation accompanying the participant's functional gains suggest that the same types of brain-behavior relationships documented in stroke survivors who receive BCI therapy may also play a role in motor recovery in stroke survivors with preexisting neurological conditions unrelated to their stroke.

With regard to the increased contralesional activity observed upon completion of the BCI therapy period (**Figure 9B**), this may be indicative of greater recruitment and coordination of contralesional brain areas during attempted finger tapping of the impaired left hand. While some studies examining changes in brain activation with BCI therapy found shifts in activity of the motor and premotor cortices toward the ipsilesional hemisphere to accompany motor gains (Caria et al., 2011; Ramos-Murguialday et al., 2013), others examining the role of the contralesional hemisphere in post-stroke recovery have shown that brain activation in the contralesional hemisphere and its functional connectivity to that of the ipsilesional hemisphere may contribute significantly to motor performance after stroke (Lotze et al., 2006; Carter et al., 2010). There have also been studies of other functional domains, such as language, where a compensatory shift in activation toward the intact hemisphere has been documented in

response to infarction and hypoperfusion (Prabhakaran et al., 2007). As these changes were observed over the same time period in which significant functional motor gains were achieved, it is possible that this pattern may reflect neuroplastic processes related to the participant's motor recovery.

While the increased contralesional activity observed after BCI therapy cannot be directly attributed to the BCI therapy, it can be distinguished from brain changes observed with repeated scanning before and after the observational control period. The increased activity in the contralesional hemisphere with BCI therapy is noticeably different from the general decrease in ipsilesional activity observed over the course of the observational control period (**Figure 9A**). These different patterns of change suggest that the increases observed during the BCI therapy period are less likely to be due to a practice effect associated with repeated scans or due to effects associated with the outside physical therapy, occupational therapy, or botox treatments the participant received during both phases of the study period. Unfortunately, as this study documents such changes in only a single subject, it cannot be determined if the pattern of increased contralteral activations observed after BCI therapy is due to the nature of the BCI device used, some neurological characteristic of this subject that may or may not generalize to other individuals with preexisting sensorineural disabilities, or some interaction of the two. Future studies are needed to clarify whether the use of BCI devices is accompanied by differential changes in neural activity in individuals recovering from stroke and to determine what quantitative relationships may exist between such changes and increases in motor function.

The relationship between what parameters are implemented during BCI therapy and how these parameters may affect functional outcomes is another area in need of further investigation. In particular, overall BCI performance accuracy in this study was consistently above chance but not significantly greater than 70%, which is a commonly used threshold for establishing adequate control of a BCI system. Although this 70% was used as a threshold for increasing task difficulty, future participants may benefit from additional training either before additional modes of feedback are applied or before game play parameters are adjusted to make the task more difficult. The optimal balance between what performance accuracy should be demonstrated as an indication of adequate feedback vs. what level of difficulty should be implemented to minimize subject fatigue and/or boredom remains to be determined. Future studies are needed to better characterize this trade off in individuals with and without preexisting disabilities.

It will be necessary in the future to continue studying subpopulations of stroke survivors in order to better understand what, if any, differences there may be in the potential benefits of BCI therapy for those with preexisting disabilities or neurological conditions compared to the benefits that such therapies may offer individuals who were neurotypical prior to stroke. With nearly 10% of adults in the United States suffering from mood disorders such as depression (Kessler et al., 2005) and approximately 30% of adults in the United States aged 65 and older reporting a visual, hearing, or cognitive disability (Institute, 2013), it is important to ensure that advances in stroke rehabilitation can be made available to stroke survivors with preexisting disabilities or neurological conditions. This case study shows that a limitation such as deafness or a preexisting diagnosis such as depression may not be sufficient grounds upon which to deny such therapies to stroke survivors in need of rehabilitation, and further research will be needed to increase the availability of such therapies to stroke survivors with persistent motor impairments both in the presence or absence of preexisting neurological conditions.

AUTHOR CONTRIBUTIONS

Brittany M. Young assisted in subject recruitment, data collection, data analysis, and writing. Zack Nigogosyan assisted with data collection and writing. Veena A. Nair assisted with subject recruitment, data collection, data analysis, and writing. Léo M. Walton assisted with data collection and writing. Jie Song assisted with subject recruitment and data collection. Mitchell E. Tyler provided TDU hardware and expertise. Dorothy F. Edwards assisted with study design and data analysis. Kristin Caldera assisted with subject recruitment. Justin A. Sattin assisted with study design. Justin C. Williams is one of two lead PI's on this project and supervised the technical and engineering aspects of the work. Vivek Prabhakaran is one of two lead PI's on this project and supervised the neuroimaging and neuroscience aspects of this work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fneng.2014.00018/abstract

Video S1 | Video of the participant's attempted hand movements during the open-loop screening task showing attempted repeated hand opening and closing for each hand as well as rest on the first day of interventional BCI therapy. Words in the bottom left corner of the screen correspond to the stimuli shown to the participant over the course of the video period. Stimuli were presented in random order. Video was taken with the camera positioned above the table facing the participant such that the participant's left hand is shown on the right side of the screen.

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Characterizing relationships of DTI, fMRI, and motor recovery in stroke rehabilitation utilizing brain-computer interface technology

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The relationship of the structural integrity of white matter tracts and cortical activity to motor functional outcomes in stroke patients is of particular interest in understanding mechanisms of brain structural and functional changes while recovering from stroke. This study aims to probe these underlying mechanisms using diffusion tensor imaging (DTI) and fMRI measures. We examined the structural integrity of the posterior limb of the internal capsule (PLIC) using DTI and corticomotor activity using motor-task fMRI in stroke patients who completed up to 15 sessions of rehabilitation therapy using Brain-Computer Interface (BCI) technology. We hypothesized that (1) the structural integrity of PLIC and corticomotor activity are affected by stroke; (2) changes in structural integrity and corticomotor activity following BCI intervention are related to motor recovery; (3) there is a potential relationship between structural integrity and corticomotor activity. We found that (1) the ipsilesional PLIC showed significantly decreased fractional anisotropy (FA) values when compared to the contralesional PLIC; (2) lower ipsilesional PLIC-FA values were significantly associated with worse motor outcomes (i.e., ipsilesional PLIC-FA and motor outcomes were positively correlated.); (3) lower ipsilesional PLIC-FA values were significantly associated with greater ipsilesional corticomotor activity during impaired-finger-tapping-task fMRI (i.e., ipsilesional PLIC-FA and ipsilesional corticomotor activity were negatively correlated), with an overall bilateral pattern of corticomotor activity observed; and (4) baseline FA values predicted motor recovery assessed after BCI intervention. These findings suggest that (1) greater vs. lesser microstructural integrity of the ipsilesional PLIC may contribute toward better vs. poor motor recovery respectively in the stroke-affected limb and demand lesser vs. greater cortical activity respectively from the ipsilesional motor cortex; and that (2) PLIC-FA is a promising biomarker in tracking and predicting motor functional recovery in stroke patients receiving BCI intervention.

Keywords: DTI, FA, fMRI, motor recovery, stroke rehabilitation, BCI

INTRODUCTION

Studies have suggested that motor recovery after stroke is related to the structural remodeling of white matter tracts (Liu et al., 2008; Schaechter et al., 2009) and the reorganization of cortical activity (Dijkhuizen et al., 2001; Jaillard et al., 2005; Grefkes et al., 2008) in the ipsilesional and contralesional hemispheres. Little is known, however, about the relationship between the white matter structural integrity and functional cortical activity of the sensorimotor region and how these two factors interact with motor recovery in stroke patients. Therefore, a multimodal assessment of structure-function relationships may provide insights for examining factors influencing stroke recovery. Noninvasive brain imaging methods have been widely applied for understanding brain recovery following stroke. Diffusion tensor imaging (DTI)

is one of these imaging methods, which allows for quantitative evaluations of the structural integrity of white matter tracts after a stroke (Werring et al., 2000; Stinear et al., 2007; Yu et al., 2009). DTI-derived measures have been shown as potential biomarkers used for tracking motor impairment (Schaechter et al., 2009; Lindenberg et al., 2010; Sterr et al., 2010; Yeo et al., 2010; Borich et al., 2012; Chen and Schlaug, 2013) and motor recovery (Liang et al., 2009) after stroke. DTI has also been investigated for its prognostic potential, with DTI measures assessed during the acute and sub-acute stages of stroke shown to predict motor impairments observed 1–7 months later (Cho et al., 2007; Koyama et al., 2012, 2013a,b; Groisser et al., 2014). A recent study shows evidence that DTI measures may be used as potentially predictive of individual recovery in stroke patients receiving newer neurorehabilitative therapies, such as transcranial direct current stimulation (Lindenberg et al., 2012). Besides DTI, fMRI is another non-invasive neuroimaging technique that has been used to gain better understanding of the processes of brain functional reorganization accompanying motor recovery after stroke (Calautti and Baron, 2003; Riecker et al., 2010; Garrison et al., 2013; Havsteen et al., 2013; Favre et al., 2014; Zhang et al., 2014). Measures derived from fMRI have also been shown as potential biomarkers to track recovery, with correlations between functional changes and fMRI measures demonstrated with treatments such as Brain-Computer Interface (BCI) therapy (Mukaino et al., 2014), constrain-induced movement therapy (Murayama et al., 2011; Kononen et al., 2012) and motor imagery therapy (Sun et al., 2013).

Fewer studies have taken a multimodal approach to characterize brain recovery after stroke by combining information from both DTI and fMRI measures, with a few attempts existing only as case studies (Jang et al., 2005; Caria et al., 2011). One recent study found that DTI-derived measures correlated more strongly with clinical outcomes than measures derived from fMRI (Qiu et al., 2011) and another study reported both DTI and fMRI derived measures correlated with motor outcomes (Chen and Schlaug, 2013). Correlations have also been identified between DTI and fMRI measures, with greater damage to white matter tracts showing an association with increased bilateral recruitment of motor areas and poorer motor performance in stroke patients (Wang et al., 2012), although there is also evidence that such correlations may be modulated after the functional electrical stimulation (FES) training (Wei et al., 2013).

In this study, one main goal is to investigate the relationship between DTI and fMRI measures and further investigate the relative contribution of each to the tracking and predicting of motor functional recovery in a group of stroke patients with persistent upper extremity impairment receiving BCI therapy. In the majority of stroke patients, the upper extremity is more severely involved than the lower limb, as most strokes occur in the territory of the middle cerebral artery (Shelton and Reding, 2001). Stroke that affects the posterior limb of the internal capsule (PLIC) has been reported to be significantly associated with poor recovery of isolated upper-limb movements (Shelton and Reding, 2001) and overall motor outcomes (Puig et al., 2011). Given the significance of PLIC involved in motor recovery, one specific aim of this study is to evaluate the stroke-induced changes in structural integrity of the PLIC using DTI fractional anisotropy (FA) and to investigate if these changes are related to motor recovery. Corticomotor activation is a fMRI way to examine the "integrity" of corticomotor functions. In this study corticomotor activity is evaluated using motor-task fMRI and quantified by counts of statistically significantly active voxels within the ipsilesional and contralesional motor cortices. Another specific aim of this study is to evaluate the changes in corticomotor activity, and to further examine if these changes are related to motor recovery. Combining both DTI and fMRI analysis, we examine the potential relationship between structural integrity of PLIC and functional integrity of motor cortex, and examine how this relationship interact with motor recovery in patients receiving BCI intervention.

MATERIALS AND METHODS

STUDY DESIGN

A permuted-block design accounting for gender, stroke chronicity and severity of motor impairment was used to randomize patients to either a BCI intervention group or a crossover control group. Neuroimaging data and motor outcome assessments were acquired at four time points: before the start of intervention (i.e., pre-intervention), at the midpoint of intervention (i.e., mid-intervention), upon completion of intervention phase (i.e., immediately post-intervention), and 1 month following the last session of BCI intervention (i.e., 1-month-post-intervention). Patients in the BCI intervention group began to receive BCI intervention soon after recruitment. Patients in the control group first received three additional neuroimaging scans and motor outcome assessments during the control phase in which no BCI intervention was administered. These three additional assessments were acquired at intervals analogous to those administered during the BCI intervention phase. Upon completion the final-control neuroimaging and motor outcome assessment, these patients were crossed over to complete the BCI intervention phase. **Table 1** illustrates the time frame of the study design. All current findings are based on neuroimaging and motor outcome measurements acquired from 9 patients *during the BCI intervention phase*.

PATIENT CHARACTERISTICS

Sixteen patients with persistent upper extremity motor impairment resulting from first-ever ischemic or hemorrhagic stroke were contacted regarding study participation in an on-going study investigating effects of EEG-BCI driven FES therapy of the impaired hand in stroke patients. This report is based on 9 patients who have completed the study (6 M, mean age of 61.9 years, chronicity of stroke range 2–23 months).

The inclusion criteria were: (1) ages 18 years and above; (2) no known neurologic, psychiatric or developmental disability; (3) persistent upper-extremity motor impairment resulting from ischemic or hemorrhagic stroke. The exclusion criteria were: (1) contraindications for MRI; (2) allergy to electrode gel, surgical tape and metals that would be used in BCI intervention; (3) under treatment for infectious disease or having apparent oral lesions or inflammation. This study was approved by the University of Wisconsin-Madison's Health Sciences Institutional Review Board.

Table 1 | Study design.

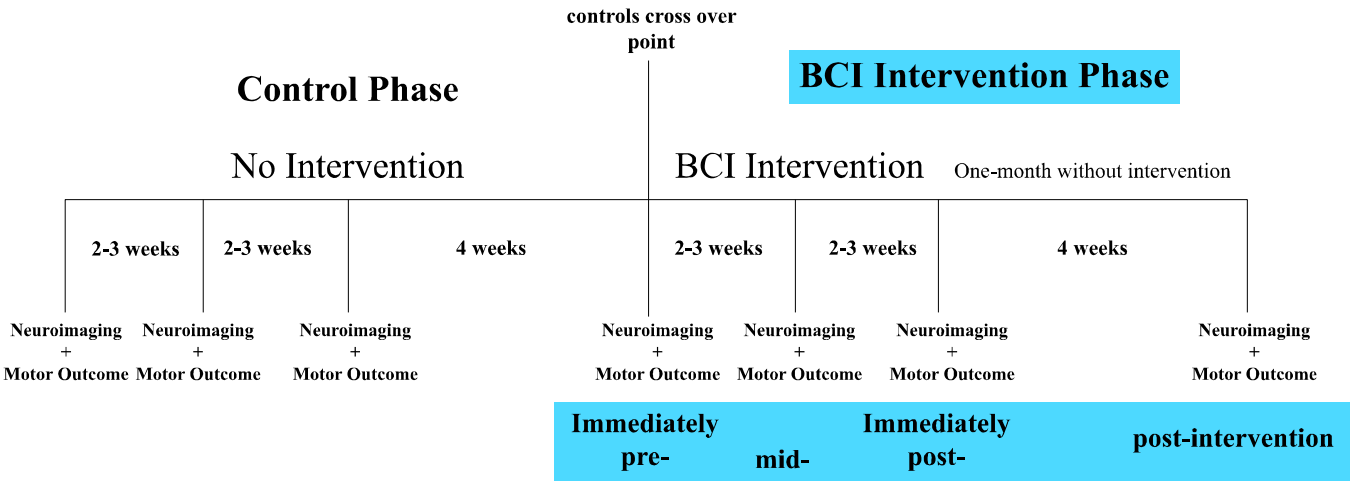

Table 2 | Patient profiles (age, gender, time since stroke, baseline NIHSS, baseline NIHSS-motor arm and stroke location).

Subject ID	Age	Gender	Months since stroke	Baseline NIHSS	NIHSS-motor arm	Stroke location
CI001	52	M	15	8	4	Left MCA
CI002	62	F	16	8	4	Left precentral gyrus
CI003	68	M	3	0	0	Left frontal lobe
CI004	66	M	23	6	1	Left MCA
CI005	73	F	2	0	0	Left MCA
CT001	75	F	23	7	3	Right putamen
CT002	55	M	17	0	0	Left basal ganglia
CT003	49	M	6	3	1	Right pons
CT004	57	M	13	2	1	Left MCA
Mean ± SD	**61.89 ± 9.25**	**3F/6M**	**13.11 ± 7.90**	**3.78 ± 3.49**	**1.56 ± 1.67**	**3 sub-cortical**

MCA, Middle Cerebral Artery.

All patients provided written informed consent. Patient profiles are shown in **Table 2**.

BCI INTERVENTION PROCEDURES

All patients were administered up to 15 two-hour sessions of interventional BCI therapy (13.11 ± 2.20 sessions). Figure S1 illustrates a conceptual schematic of the system. A detailed description of the procedures followed during each session is provided in the Supplementary Material. These sessions took place over a period of up to 6 weeks with two to three intervention sessions per week.

MOTOR FUNCTIONAL OUTCOME MEASURES

All patients were assessed for clinical stroke severity in addition to neurologic examination at four time points throughout the intervention (**Table 1**). The neurologic deficit was evaluated on the basis of the severity of motor paresis using the National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989). All patients' motor function of the impaired arm was assessed using a neuropsychological battery which included objective measures such as the Action Research Arm Test (ARAT) (Carroll, 1965; Lang et al., 2006) and subjective measures such as the Stroke Impact Scale-Hand function domain (Duncan et al., 1999). The ARAT is a standardized measure of upper-limb functioning assessing grip, grasp, pinch and gross motor performance. Total ARAT scores ranged from 0 to 57. The Stroke Impact Scale (SIS) hand function subscale (SIS-Hand) was used to assess self-reported satisfaction with hand use and to evaluate the relationship between SIS-Hand scores and neuroimaging measures. Raw scores of SIS-Hand assessment were transformed using the following algorithm (Sullivan, 1995): Transformed scale = 100 × [(actual raw score − lowest possible raw score)/possible raw score]. The transformed scale of SIS-Hand score ranged from 0 to 100. All clinical assessments of the stroke-affected limb for each patient at each time point are shown in Table S3.

NEUROIMAGING DATA

Neuroimaging data acquisition and processing are described in detail in the Supplementary Material. FA values were computed for the ipsilesional and contralesional PLIC. In addition, asymmetry indices between the ipsilesional and contralesional PLIC-FA (aFA) were calculated as $aFA = (FA_{contra} - FA_{ipsi})/(FA_{contra} + FA_{ipsi})$ (Stinear et al., 2007; Schaechter et al., 2009; Lindenberg et al., 2010). This yields a value of aFA ranging from −1.0 to +1.0

with positive values indicating reduced FA in the ipsilesional PLIC, a value of 0 indicating symmetrical FA measurements from the two hemispheric PLIC, and a negative value indicating reduced FA in the contralesional PLIC.

All patients performed a block-design sequential finger tapping task during fMRI scans that consisted of alternating 20-s blocks of tapping vs. rest. Patients were cued to rest or to tap the fingers of one hand sequentially on a button box, using either visual or tactile (for visually impaired patients) cues. All patients underwent two fMRI scans using this paradigm –once when tapping with the impaired hand (passive tapping if unable to generate sufficient tapping independently) and again when tapping with the unimpaired hand. Patients were instructed to hold their heads still throughout the scans, and sufficient padding was provided to discourage head movement.

In the passive motor tasks, patients were assisted by the investigator in finger movements (flexion-extension) to complete the finger tapping tasks according to the experimental paradigm design.

MOTOR-TASK GENERATED ACTIVE VOXELS

A previously published mask of the cortical components of the motor network was used to identify statistically significantly active voxels in the motor cortex during finger tapping. This mask consisted of the cortical components of a previously identified motor network derived from an independent component analysis (ICA) of whole-brain resting-state fMRI (rs-fMRI) scans (Shirer et al., 2012). These independent components were visually selected based on previous reports and then thresholded independently and arbitrarily to generate distinct moderately sized ROIs in the cortex and subcortical gray matter (voxels = 25) (Shirer et al., 2012). It is worth noting that although rs-fMRI investigates synchronous activations between brain regions occurring in the absence of a task or stimulus, these synchronous activations have been observed in somatosensory, visual, attention and other higher-order brain areas and have shown close correspondence between the independent analyses of resting and activation brain dynamics (Biswal et al., 1995; Smith et al., 2009). In our study, only the cortical components from the motor network for each hemisphere were used for evaluation of corticomotor activity. Once fMRI data was processed (see Supplementary Material), this motor cortical mask was resampled into subject space and then applied to the functional data to identify those statistically significantly active voxels within the motor cortex using a threshold of $t = 4$ ($p < 0.0001$).

STATISTICAL ANALYSIS

Considering the relatively small sample size ($n = 9$), we used non-parametric statistical tests for the analyses. The Wilcoxon signed-rank test was used to compare ipsilesional and contralesional PLIC FA values and to compare corticomotor fMRI activity between the two motor cortices. The Spearman rank correlation test was used for analyses of neuroimaging and motor outcome measurements. To take advantage of a longitudinal, repeated-measurement design of this study, we used generalized estimating equations (GEE) for regression analyses. GEE analyses use the generalized linear model to estimate more efficient and unbiased regression parameters relative to ordinary least squares regression (Ballinger, 2004). Most importantly, the GEE analyses take into account the dependency of repeated measurements from the same patient in the regression analysis. In addition, ANOVAs were used to examine how factors of time (pre-, mid-, immediately post-, and 1-month-post), PLIC (contralesional vs. ipsilesional side) and interaction between time and PLIC affecting DTI and fMRI measures. All statistical analyses were performed using RStudio (version 0.97.318). A p value less than or equal to 0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS AND CLINICAL MEASURES

Patient characteristics are summarized in **Table 2**. Average age was 61.89 years ($SD = 9.25$ years); average time from stroke onset was 13.11 months ($SD = 7.90$ months). There were no significant differences in terms of left or right hemisphere stroke ($p = 0.14$), cortical or non-cortical stroke ($p = 0.36$), or gender ($p = 0.36$). Standard clinical MRI was used to assess damage to PLIC by the neuroradiologist Dr. Prabhakaran. Six of the nine patients showed damage to PLIC due to stroke. Patient CT004 with a left middle cerebral artery (MCA) territory infarct showed minimal damage to PLIC. Patients CI003 with a small left frontal lobe infarct and CT003 with a right pontine infarct did not show damage to PLIC.

Clinical motor outcome measures are summarized in Table S3. The ARAT scores varied from zero, indicating no ability to perform, to a maximum of 57, indicating unimpaired performance. The SIS measure of hand function varied widely, with a value of zero indicating a patient reporting no ability to use the impaired hand, and higher positive values indicating decreasing levels of difficulty using the impaired hand in daily activities such as carrying heavy objects, turning a doorknob, opening a can or jar, tying a shoe lace and picking up a dime.

RELATIONSHIP OF PLIC-DTI MEASURES AND MOTOR OUTCOMES

An ANOVA was computed to examine the main effects of time and PLIC (contralesional vs. ipsilesional side) as well as time × PLIC interaction (**Figure 1A**). Only PLIC factor was significant ($p = 5.56e\text{-}07$), and this was further validated with a Wilcoxon signed-rank test. Ipsilesional PLIC FA values were significantly lower when compared to the contralesional side (Wilcoxon signed-rank test: $p < 0.05$) except at time point 3 (immediately post-intervention) with a p-value equal to 0.055 trending toward significance (**Figure 1B**).

To assess the relationship between PLIC-FA values and motor outcome measures, a Spearman rank correlation test was first performed on the longitudinal data acquired from all patients and from all time points. The results suggested that higher ARAT scores and higher SIS-Hand scores were significantly correlated with higher FA values in ipsilesional PLIC (**Figure 2**). PLIC FA asymmetry (aFA) was negatively correlated with ARAT and SIS-Hand scores (**Figure 2**). A secondary statistical analysis, the GEE analysis, was further computed to control for the dependence of repeated measurements from each patient across time (**Table 3**). This analysis confirmed that the relationship observed between PLIC-FA and motor outcomes remained statistically significant. In addition, stroke severity as assessed by the NIHSS

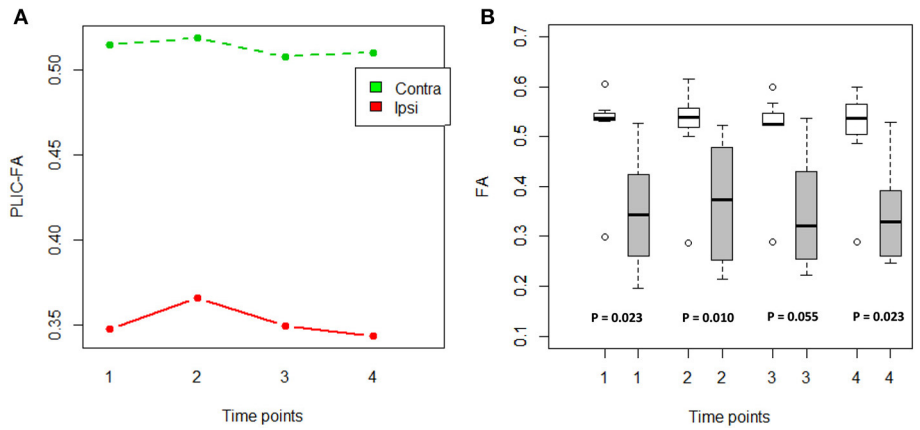

FIGURE 1 | FA values compared between the ipsilesional and contralesional sides of the PLIC. (A) PLIC-FA changes across time compared between two hemispheres using ANOVA tests. Contra, contralesional PLIC; Ipsi, ipsilesional PLIC. **(B)** Boxplots showed significantly lower FA in ipsilesional PLIC when compared to contralesional PLIC (Time of pre-, mid-, post-, and 1-month-post intervention are indicated as time-point 1, 2, 3, and 4, respectively). White boxes represent the contralesional side and gray boxes represent the ipsilesional side of PLIC. (Wilcoxon signed-rank tests; all *p*-values are listed).

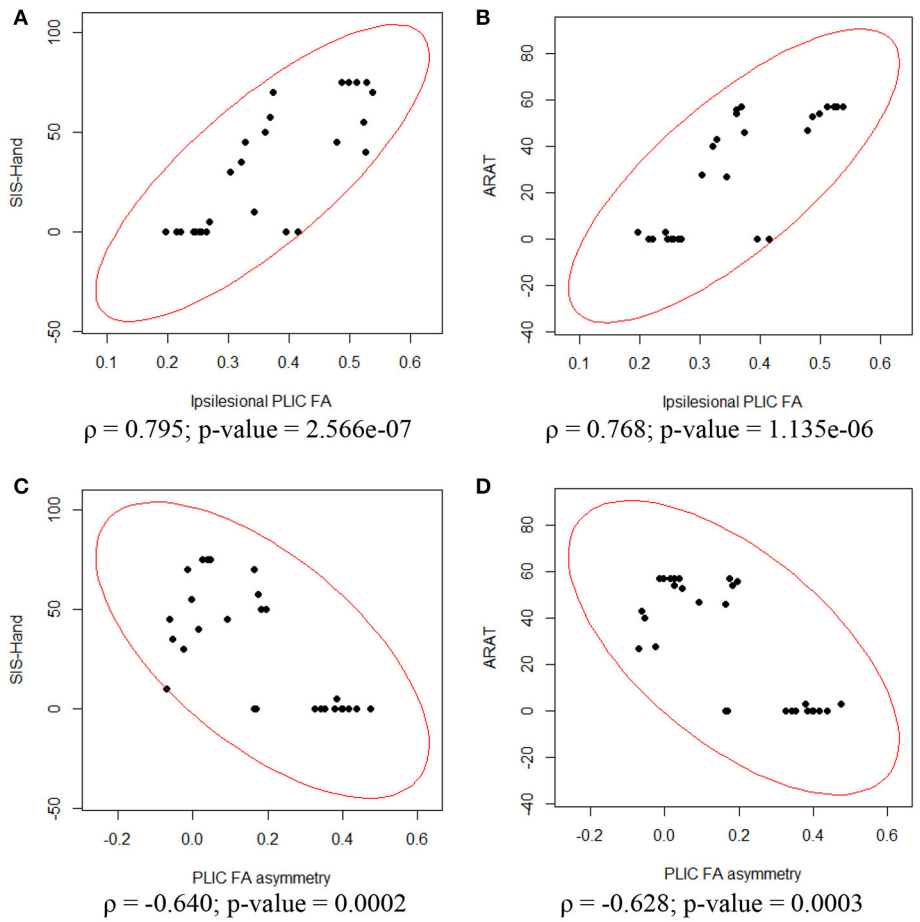

FIGURE 2 | Correlation analyses between ipsilesional FA, aFA and motor outcomes assessed in the impaired hand. Spearman rank correlation tests showed significant relationships between DTI and motor outcome measurements. **(A)** Ipsilesional PLIC-FA was positively correlated with SIS-hand function. **(B)** Ipsilesional PLIC-FA was positively correlated with ARAT. **(C)** PLIC-aFA was negatively correlated with SIS-hand function. **(D)** PLIC-aFA was negatively correlated with ARAT.

Table 3 | Correlation analyses of DTI, fMRI and motor recovery measures.

(A) SPEARMAN RANK CORRELATION TESTS ON NEUROIMAGING AND MOTOR OUTCOME MEASURES				
Motor outcomes	**Spearman rank correlation test**	**FA**	**aFA**	**Voxel counts**
SIS-Hand	correlation coefficient	0.795	−0.640	−0.463
	p-value	2.566e-07	0.0002	0.012
ARAT	correlation coefficient	0.768	−0.628	−0.414
	p-value	1.135e-06	0.0003	0.026
(B) GEE REGRESSION ANALYSES BETWEEN NEUROIMAGING AND MOTOR OUTCOME MEASURES				
Motor outcomes	**GEE**	**FA**	**aFA**	**Voxel counts**
SIS-Hand	Regression coefficient	229.89	−138.47	−0.01
	p-value	**1e-06**	**6.86e-10**	0.55
ARAT	Regression coefficient	127.93	−116.50	−0.03
	p-value	**0.001**	**6.68e-09**	0.27

was significantly and negatively correlated with ipsilesional PLIC-FA values (**Figure 3**; GEE regression coefficient = −33.57, *p*-value = 3.69e-04).

PREDICTION OF MOTOR FUNCTION RECOVERY WITH BASELINE NEUROIMAGING MEASURES

The linear regression analyses using a least-square fitting method revealed that baseline ipsilesional PLIC-FA correlated with the post-intervention ARAT and SIS-Hand scores (**Figure 4**; r-squared values > 0.7). Ipsilesional PLIC FA values measured at pre-intervention (baseline) were significantly and positively correlated with motor outcome scores measured immediately post- and 1-month-post intervention (*p*-value = 0.05). The same approach was applied to fMRI voxel counts, which did not reveal a predictive relationship with this fMRI measure on motor recovery.

RELATIONSHIP OF CORTICOMOTOR ACTIVITY AND MOTOR OUTCOMES

For the impaired finger tapping task, counts of active voxels were not significantly different between the two motor cortices (Wilcoxon signed-rank test: $p = 0.28$) (**Figure 5A**). Note, passive motor-task fMRI data was collected for patients CI001, CI002, CI004, CT001, and CT003 who were unable to perform motor tasks during fMRI scans. For the unimpaired finger tapping task, active voxel counts were significantly greater within contralesional motor cortex compared with the ipsilesional side (Wilcoxon signed-rank test: $p = 0.038$) (**Figure 5B**). An ANOVA was computed to examine the effects of time and PLIC (contralesional vs ipsilesional side) and the time × lesion interaction for both fMRI measures from impaired and unimpaired finger tapping. The results revealed no significant changes in corticomotor activity due to any of these factors (**Figures 5C,D**). However, the influence of PLIC trended toward significance ($p = 0.064$) for the unimpaired finger tapping task.

Given the changes observed in corticomotor activity across time for impaired finger tapping compared to unimpaired finger tapping, another ANOVA was computed to test the effects of time (pre-, mid-, immediately post- and 1-month-post), PLIC (contralesional vs. ipsilesional), hand-impairment (impaired vs. unimpaired), and interaction between time and hand-impairment. We found that both the effect of hand-impairment and interaction between time and hand-impairment were significant (*p*-value = 0.005 and 0.015 respectively).

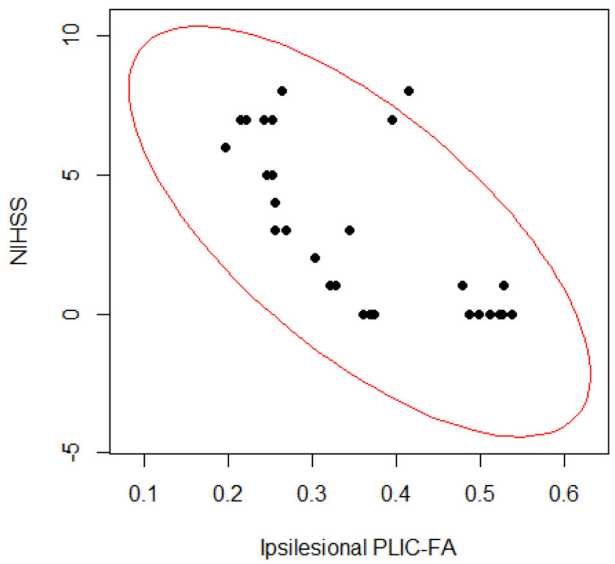

FIGURE 3 | Correlation analyses on stroke severity (NIHSS scores) and structural integrity of PLIC (FA values). The Spearman rank correlation test ($\rho = -0.695$; *p*-value = 2.892e-05) and GEE regression analysis (GEE *p*-value = 3.691e-04) showed significant relationships between PLIC-FA values and patients' clinical severity assessments (NIHSS scores).

The Spearman rank correlation tests also demonstrated that fMRI measures (i.e., active voxel counts in ipsilesional motor cortex generated from impaired finger tapping task) were associated with motor outcomes. This negative association between motor outcomes and fMRI measurements may suggest that better motor outcomes after BCI-intervention are associated with a smaller number of active voxels within the ipsilesional motor cortex (Figure S2). However, this relationship was no longer significant after GEE regression analyses accounted for the dependence of repeated measurements from each patient (**Table 3**).

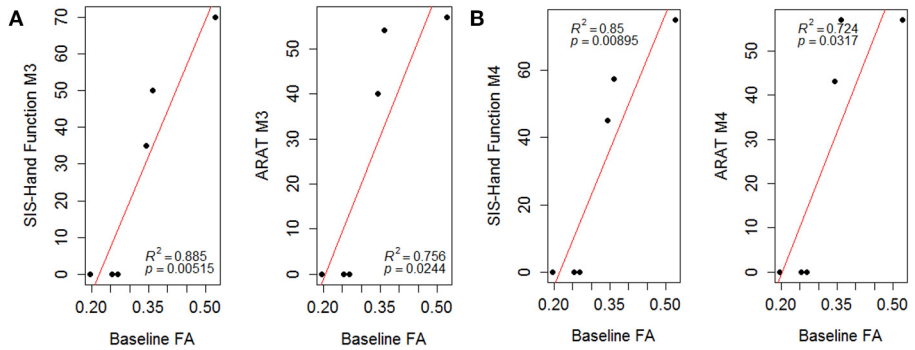

FIGURE 4 | Scatter plots of PLIC-FA predicting motor outcomes evaluated (A) immediately post-intervention (M3) and (B) 1-month-post intervention (M4). Linear regression analyses demonstrated that baseline PLIC-FA can predict motor outcomes. Pearson's correlation coefficients (ρ) and r-squared (R^2) values are shown on the figures.

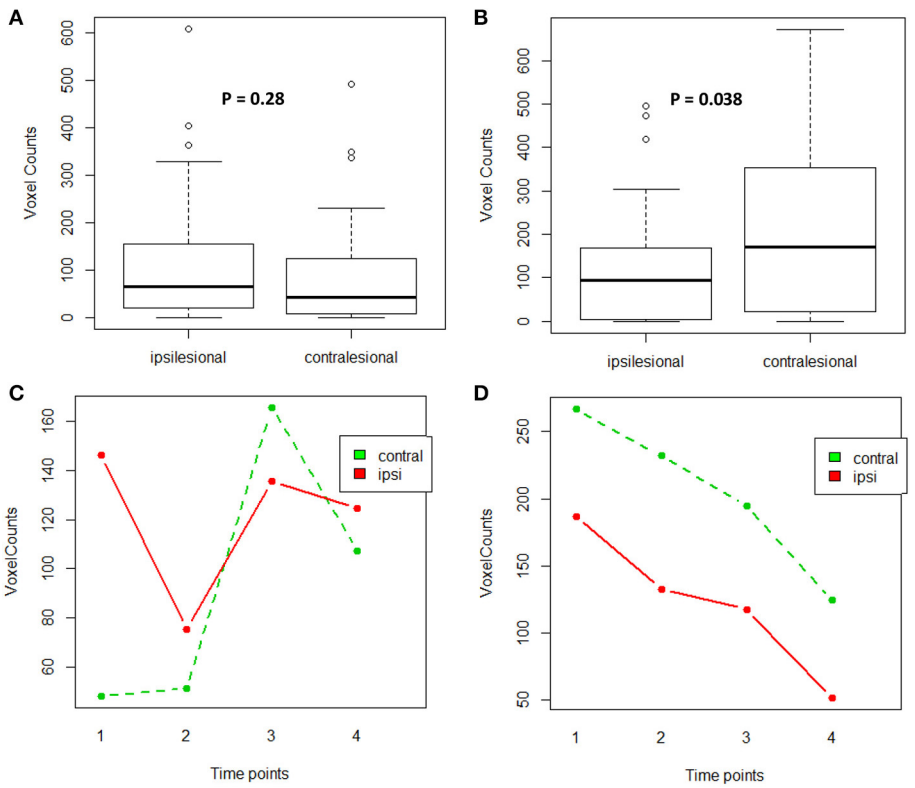

FIGURE 5 | Comparison of active voxel counts during impaired and unimpaired finger tapping during fMRI scans. (A) Impaired finger tapping condition examining lesion factor, **(B)** Unimpaired finger tapping condition examining lesion factor, **(C)** Impaired finger tapping condition examining both lesion and time factors, **(D)** Unimpaired finger tapping condition examining both lesion and time factors.

RELATIONSHIP BETWEEN DTI AND fMRI MEASUREMENTS

The corticospinal pathway from the primary motor cortex through the PLIC approaches the midline of lower medulla oblongata and crosses to the contralateral side at the pyramidal decussation (Vulliemoz et al., 2005). A small percentage of fibers (10–25%), however, remain ipsilateral (Davidoff, 1990). A schematic illustration of the PLIC and motor cortex is shown in **Figure 6**. Taking this fact into account, we examined the DTI-fMRI relationship within each hemisphere for both impaired and unimpaired finger tapping tasks. The Spearman rank correlation test followed by GEE was used for correlation analyses.

For the impaired finger tapping, crossing fibers form the majority of ipsilesional PLIC, and may be affected by the small percentage of PLIC fibers on the contralesional side (Vulliemoz et al., 2005). We found that ipsilesional PLIC-FA negatively correlated with active voxel counts within the ipsilesional motor

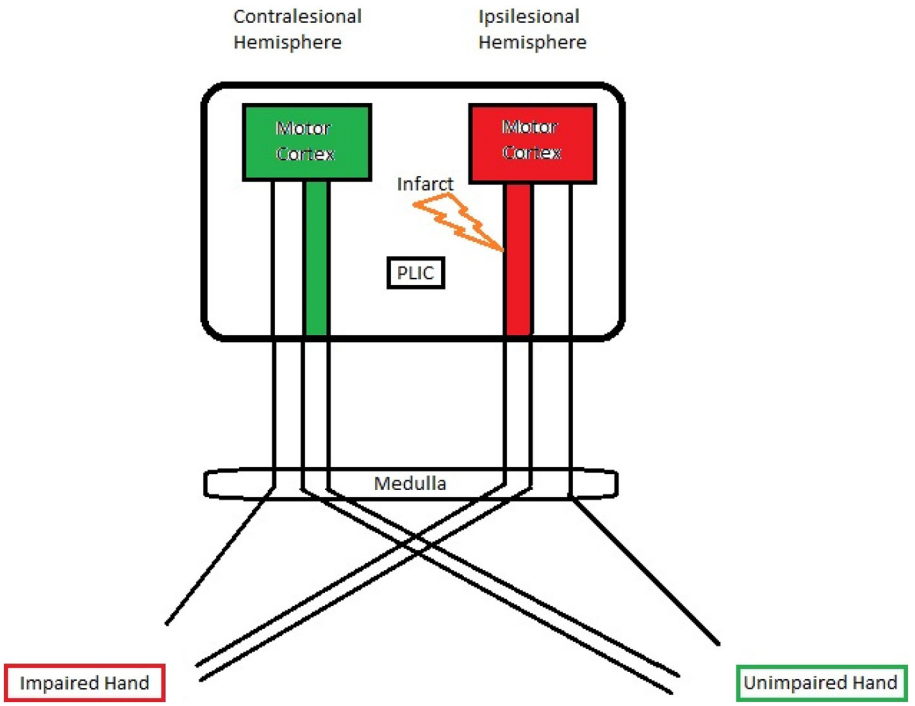

FIGURE 6 | A schematic illustration of the PLIC and motor cortex. A significant negative correlation was observed between ipsilesional PLIC-FA and ipsilesional motor activity.

cortex (**Figure 7**). We did not, however, observe a significant relationship between contralesional PLIC-FA and voxel counts within the contralesional motor cortex. A similar approach was applied for measurements from unimpaired finger tapping. No significant relationship was found between PLIC-FA and voxel counts within ipsilesional or contralesional hemisphere during unimpaired finger tapping.

DISCUSSION

Much of the focus of fMRI in stroke studies has been on whether its application provides a better understanding of brain functional reorganization accompanying motor recovery after stroke (Riecker et al., 2010; Garrison et al., 2013; Havsteen et al., 2013; Heiss and Kidwell, 2014). In a recent study, fMRI-derived measures have been correlated with movement recovery achieved with robot-assisted BCI therapy (Varkuti et al., 2013), while another study found that fMRI measures do not contribute significantly to the prediction of motor recovery (Zarahn et al., 2011). Another non-invasive MRI-based technique, DTI, has been widely used to evaluate the integrity of the white matter tracts after stroke. DTI-derived measures have been shown to be potential biomarkers for tracking motor impairment (Lindenberg et al., 2010; Chen and Schlaug, 2013) and motor recovery (Liang et al., 2009) after stroke. This study investigated the relationship between white matter integrity evaluated by DTI FA at the PLIC and corticomotor activity measured by motor-task fMRI, and further examined if these imaging measurements correlate with motor functional recovery in stroke patients receiving a BCI-facilitated intervention. Although our findings are preliminary and based on a moderate-size dataset, we observed consistent and robust results which are discussed here.

STRUCTURAL INTEGRITY OF THE PLIC VS. MOTOR RECOVERY

Previous human and animal studies have characterized changes in FA in the corticospinal system due to stroke (Liu et al., 2007; Kusano et al., 2009; Schaechter et al., 2009; Lindenberg et al., 2012). In our study, DTI analyses on 9 stroke patients with varying lesion locations and size of infarct affected the corticospinal system and yielded consistent observations, specifically, decreased FA in the ipsilesional PLIC compared to the contralesional side. This has been suggested as a characteristic of chronic white matter "Wallerian" degeneration (Yu et al., 2009; Lindenberg et al., 2012) and is thought to arise from the loss of tissue structural integrity (Liu et al., 2007).

In the current study, we found that higher ARAT and SIS-Hand scores were significantly correlated with higher FA values measured within ipsilesional PLIC after accounting for repeated measurements (**Table 3**). To account for potential changes in contralesional PLIC, FA asymmetry between the ipsilesional and contralesional sides were calculated (Stinear et al., 2007; Lindenberg et al., 2010) and then correlated with motor outcome measurements. The relationship between FA asymmetry and motor outcomes was significant even when accounting for repeated measurements. Lower or near zero aFA values indicate better preserved integrity of the ipsilesional PLIC and were correlated with better motor outcomes. Given our observation

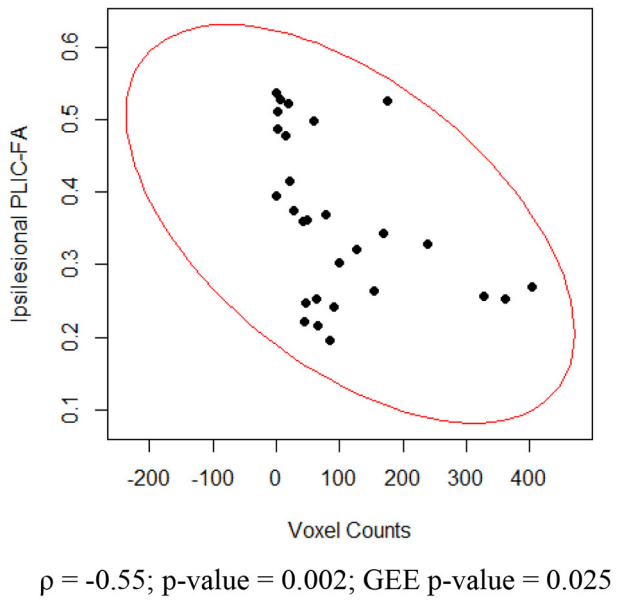

FIGURE 7 | Relationship between ipsilesional corticomotor activity and ipsilesional PLIC-FA. Shown here are Spearman rank correlation coefficient (ρ) and corresponding *p*-value as well as GEE *p*-value.

that the ipsilesional PLIC had decreased FA compared with the contralesional side, these findings suggest that the more the ipsilesional PLIC-FA resembled the contralesional PLIC, the greater the potential for functional recovery in stroke-affected limb.

PREDICTIVE VALUE OF THE PLIC-FA IN MOTOR RECOVERY

One novel finding of this study is the predictive value of PLIC-FA in predicting recovery of motor function. Baseline FA values were significantly correlated with motor outcomes measured after intervention both immediately post-intervention and 1-month-post intervention (**Figure 4**). This suggests PLIC-FA may be useful as a novel biomarker to predict upper-limb motor functional recovery of stroke patients receiving BCI interventions.

CORTICOMOTOR ACTIVITY

For impaired finger tapping, we observed a bilateral pattern of corticomotor activity (**Figure 5A**), while unimpaired finger tapping produced significantly more lateralized activity within the contralesional motor cortex in comparison to ipsilesional motor cortex (**Figure 5B**). When comparing corticomotor activity for impaired and unimpaired finger tapping, we observed a significant difference due to the factor of hand-impairment (ANOVA test, p-value $= 0.005$). Furthermore, the pattern of changes in voxel counts (i.e., interaction between factors of time and hand-impairment) was also significant between the two tapping conditions (ANOVA test, p-value $= 0.015$). These findings may suggest that a potential bilateral pattern of corticomotor activity evolved during motor recovery in these stroke patients receiving BCI intervention.

CORTICOMOTOR ACTIVITY VS. STRUCTURAL INTEGRITY OF THE PLIC

Our results are that greater stroke severity is significantly correlated with compromised PLIC in the ipsilesional hemisphere (**Figure 3**). Furthermore, the ipsilesional PLIC-FA values are negatively correlated with ipsilesional corticomotor activity during impaired finger tapping (**Figure 7**). Thus, a greater burden of cortical activation is placed on the ipsilesional motor cortex for impaired finger tapping in patients with greater stroke severity with an overall bilateral pattern of motor cortical involvement. The BCI intervention may contribute to the increased utilization of ipsilesional and contralesional motor cortex with more bilateral activity seen during impaired finger tapping, rather than the lateralized activity seen normally during unimpaired finger tapping (**Figures 2A,B**). These factors may ultimately place demands on both ipsilesional and contralesional motor cortices during stroke recovery. This is novel in comparison to previous studies that suggest successful therapeutic intervention produces restoration of motor function mediated by re-lateralization of motor cortical activation (Ward et al., 2003a,b; Saur et al., 2006; Schlaug et al., 2008).

LIMITATIONS

The small sample size ($n = 9$) and the heterogeneity of stroke patients (**Table 2**) were the primary limitations of this study. Four of the 9 patients exhibited no or little improvement in functional recovery as assessed by clinical behavioral performance. Those patients were severely impaired and minimally able to perform the designed intervention tasks, resulting in a floor effect in some outcome measurements. While changes in fMRI and DTI measurements were observed across time, an ANOVA did not show these changes to be significant, which may also be due to small sample size and high between-patient variance. It is also worth noting that our current findings are preliminary and are based on a moderate-size dataset.

Another limitation of our study is the combined analysis of passive and active finger tapping tasks performed by these patients. Passive vs. active tasks may have different effects on corticomotor activity which was further described and discussed in Supplementary Material.

Current DTI techniques remain limited in their ability to untangle the mix of PLIC fibers from the ipsilateral and contralateral hemispheres as they descend along the corticospinal pathway. Although we used task fMRI with each hand to investigate the structure-function relationship of the PLIC and the motor cortex, the current study design does not allow us to separate the mixture of white matter tracts from ipsilateral and contralateral corticospinal pathways within the PLIC which constrains our current findings. Future studies may therefore need to be done utilizing high resolution DTI and tractography techniques to further investigate the relationship between structural and functional changes in stroke patients.

AUTHOR CONTRIBUTIONS

Jie Song assisted with subject recruitment, data collection, data analysis, and writing. Brittany M. Young assisted with subject recruitment, data collection, data analysis, and writing. Zack Nigogosyan assisted in data collection and data analysis. Leo M.

Walton assisted with data collection. Veena A. Nair assisted with subject recruitment, data collection, data analysis, and writing. Scott W. Grogan assisted with data collection and data analysis. Mitchell E. Tyler provided TDU hardware and expertise. Dorothy Farrar-Edwards assisted with study design and outcome measure selection and interpretation. Kristin E. Caldera assisted with subject recruitment. Justin A. Sattin assisted with study design and subject recruitment. Justin C. Williams is one of two lead PI's on this project and supervised the technical and engineering aspects of the work. Vivek Prabhakaran is one of two lead PI's on this project and supervised the neuroimaging aspects of this work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fneng.2014.00031/abstract

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Conflict of Interest Statement: There is one patent pending on the closed-loop neurofeedback device used for the BCI-facilitated intervention administered in this study (Pending U.S. Patent Application No. 12/715,090). This patent was filed jointly by the two lead investigators Justin C. Williams and Vivek Prabhakaran. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Changes in functional brain organization and behavioral correlations after rehabilitative therapy using a brain-computer interface

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This study aims to examine the changes in task-related brain activity induced by rehabilitative therapy using brain-computer interface (BCI) technologies and whether these changes are relevant to functional gains achieved through the use of these therapies. Stroke patients with persistent upper-extremity motor deficits received interventional rehabilitation therapy using a closed-loop neurofeedback BCI device ($n = 8$) or no therapy ($n = 6$). Behavioral assessments using the Stroke Impact Scale, the Action Research Arm Test (ARAT), and the Nine-Hole Peg Test (9-HPT) as well as task-based fMRI scans were conducted before, during, after, and 1 month after therapy administration or at analogous intervals in the absence of therapy. Laterality Index (LI) values during finger tapping of each hand were calculated for each time point and assessed for correlation with behavioral outcomes. Brain activity during finger tapping of each hand shifted over the course of BCI therapy, but not in the absence of therapy, to greater involvement of the non-lesioned hemisphere (and lesser involvement of the stroke-lesioned hemisphere) as measured by LI. Moreover, changes from baseline LI values during finger tapping of the impaired hand were correlated with gains in both objective and subjective behavioral measures. These findings suggest that the administration of interventional BCI therapy can induce differential changes in brain activity patterns between the lesioned and non-lesioned hemispheres and that these brain changes are associated with changes in specific motor functions.

Keywords: brain-computer interface, stroke rehabilitation, laterality index, LI, BCI therapy, UE motor recovery, fMRI

INTRODUCTION

Stroke remains a growing source of disability, with nearly 800,000 individuals in the United States alone experiencing a stroke each year and a projected increase of 22% in stroke prevalence by 2030 (Go et al., 2013). Despite increases in stroke incidence, stroke deaths have declined in recent years (Go et al., 2013), such that the majority of stroke patients survive their initial stroke event. Individuals in this growing population of stroke survivors are often left with persistent functional deficits. One common deficit is the acquisition of a lasting motor impairment, with up to 50% of stroke survivors suffering from some degree of hemiparesis and 26% needing assistance with activities of daily living (ADLs) 6 months post-stroke (Kelly-Hayes et al., 2003).

It has long been known that most patients experience some amount of spontaneous functional recovery shortly after stroke, with additional improvements that may be gained through the use of rehabilitative therapies in the months following the stroke event. Current guidelines note that there exists a lack of evidence to guide the optimal selection of a particular type, intensity, and amount of rehabilitative motor therapy for stroke survivors (Miller et al., 2010), and many stroke patients reach a functional plateau before complete recovery is achieved despite the use of currently available standard rehabilitative therapies. However, studies have suggested that clinically relevant plasticity and recovery potential still persist even after this plateau has been reached and that it may be possible to harness this reserve of recovery potential through the use of alternative, non-traditional therapies (Cramer, 2010) that incorporate components such as virtual reality (Orihuela-Espina et al., 2013), robot-assisted movement therapy (Lo et al., 2010; Pinter et al., 2013), and constraint-induced

movement therapy (CIMT) (Johansen-Berg et al., 2002a; Moss and Nicholas, 2006; Gauthier et al., 2008; Wolf et al., 2008, 2010; Dromerick et al., 2009; Volpe et al., 2009; Lang et al., 2013).

Another of these alternative non-traditional therapies that shows promise in stimulating additional recovery in stroke patients incorporates devices that use an emerging type of technology called brain-computer interface (BCI). EEG-based BCI is a developing technology that detects neural activity and can use these signals as a means of providing real-time feedback by which users may learn to modulate their brain activity. It has been shown that people with disabilities have no greater mental workload compared to healthy controls when using BCI devices (Felton et al., 2012), making the potential for BCI therapy in stroke patients with persistent motor disabilities both appropriate and accessible. Currently, BCI technology is being incorporated into a new class of devices intended to facilitate motor recovery in stroke patients, and early studies are beginning to show potential functional benefits associated with the use of these devices (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Liu et al., 2012; Takahashi et al., 2012). One of the motivations behind this emerging trend is the idea that BCI technology may provide a means of promoting neuroplastic change, harnessing the recovery potential that remains once patients have reached a functional plateau with standard therapies.

There is reason to believe that therapy using BCI devices may produce changes in brain activation patterns concurrent with observed behavioral changes. Such changes have been observed using other interventional rehabilitative approaches in stroke patients (Carey et al., 2002; Gauthier et al., 2008; Richards et al., 2008), and changes in brain activity patterns after stroke have also been associated with functional gains in stroke patients who experience spontaneous recovery (Ward et al., 2003). Since BCI therapies provide real-time feedback to the user, effectively rewarding the consistent production of some patterns of brain activity relative to others in the context of an intended task, there may be observable changes in the brain activation patterns produced when attempting tasks similar to those trained with BCI therapy. While this theoretical knowledge supports the possibility of inducing changes in brain activation through BCI therapy, little is yet known about the specific patterns of brain change induced in stroke patients by therapies that incorporate BCI devices.

Brain changes can be measured by laterality index (LI)– a means of quantifying the degree to which a particular task or function is lateralized between the two hemispheres of the brain. LI can be used as a measure of functional brain organization (Kundu et al., 2013) and has been used to examine functional brain reorganization in stroke patients with motor deficits using other therapy modalities. For example, LI calculations have shown repetitive transcranial magnetic stimulation therapy to produce increased laterality toward the lesioned hemisphere in those with bilateral LI at baseline (Yamada et al., 2013). Improved function has also been observed with increases in laterality toward the lesioned hemisphere after mirror therapy (Bhasin et al., 2012) or CIMT (Johansen-Berg et al., 2002a), and recruitment of contralesional motor areas has been associated with better functional improvements after gesture therapy (Orihuela-Espina et al., 2013). Still other studies of neuroimaging after rehabilitative motor therapy using such approaches have shown functional gains in the absence of detectable differences in LI after constraint-induced movement (Kononen et al., 2012) or robot-assisted (Pinter et al., 2013) therapies. Whether these conflicting patterns of change across studies represent underlying differences in the populations studied, differential effects to various interventional therapy modalities producing the functional gains, or other confounding effects remains a question that has yet to be definitively answered.

Studies that have examined changes in brain activity after BCI combined with other therapies in these patients have found brain-behavior correlations in the context of functional connectivity and its relationship to the rate at which individuals achieved gains in motor function using a BCI-robotics treatment protocol (Varkuti et al., 2013) as well as in the association between LI changes and motor function improvements using a BCI-physiotherapy treatment protocol (Caria et al., 2011; Ramos-Murguialday et al., 2013). However, such BCI studies and analyses to date remain few and limited in the context of combined therapies. The aim of the present study was to investigate the effect of interventional therapy using a closed-loop neurofeedback BCI device intended to improve motor function in stroke patients on task-derived patterns of brain activation and to assess whether any observable changes in these activation patterns correlated to changes in behavioral outcomes. We examined subjective and objective measures of motor function and obtained fMRI scans of brain activation patterns during a finger tapping task at four different time points with and without the administration of BCI therapy. We hypothesized that changes in brain activation during tapping would be observable with the administration of BCI therapy. We also examined the relationship between changes in LI with gains in motor function, hypothesizing that changes observed in LI would correlate with changes in motor function.

MATERIALS AND METHODS

RECRUITMENT METHODS AND EXCLUSION CRITERIA

Patients with persistent upper extremity motor impairment resulting from first-ever ischemic or hemorrhagic stroke were contacted regarding study participation after being identified as appropriate for participation in the study by one or more physicians responsible for their care at the University of Wisconsin Hospital and Clinics. Exclusion criteria included concurrent diagnoses of neurodegenerative disorders (e.g., dementia), other neurological or psychiatric disorders (e.g., epilepsy, schizophrenia, substance abuse), or cognitive deficits that would preclude the ability to provide informed consent. Subjects were also excluded if they had any allergies to electrode gel, surgical tape, or metals, had undergone treatment for recent infectious diseases, had apparent lesions or inflammation of the oral mucosa, were pregnant or likely to become pregnant during the course of the study, or had any contraindications to MRI.

ETHICS STATEMENT

All subjects provided written informed consent. This study, including all measures assessed and therapies administered, was

approved by the Health Sciences Institutional Review Board of the University of Wisconsin–Madison.

RANDOMIZATION AND STUDY PARADIGM

A permuted-block design accounting for gender, stroke chronicity, and severity of motor impairment was used to randomize subjects to either a BCI therapy group or a crossover control group. Subjects assigned to the BCI therapy group began participation in the BCI therapy phase of the study and received interventional rehabilitation therapy using the BCI system with functional assessment and MRI scanning at four time points: before the start of BCI therapy, at the midpoint of BCI therapy, upon completion of all BCI therapy, and 1 month following the last BCI therapy session. Subjects assigned to the crossover control group first received three additional functional assessments and MRI scans during the control phase of the study in which no BCI therapy was administered, with assessments spaced at intervals analogous to those administered during the BCI therapy phase of the study. Upon completion of the control phase of the study, subjects in the crossover control group crossed over to complete the BCI therapy phase of the study. This study paradigm is summarized in **Figure 1**.

FUNCTIONAL ASSESSMENTS

Subjects' motor function of the impaired arm was assessed using a neuropsychological battery which included both subjective and objective measures. These measures included the Stroke Impact Scale 3.0 (SIS), which is a self-report measure used to assess the ability of a stroke survivor to perform in the domains of strength, hand function, activities of daily living, mobility, communication, emotion, memory and thinking, and participation (Duncan et al., 1999; Carod-Artal et al., 2008). For this study, scores from the Hand Function domain of the SIS were of particular interest, as the BCI therapy administered is designed to promote motor rehabilitation of the upper extremity. Also assessed were subject performance on the Action Research Arm Test (ARAT), which is a standardized series of scored movements designed to evaluate upper extremity motor function in the domains of grip, grasp, strength, and gross movement (Carroll, 1965; Lang et al., 2006), and the Nine-Hole Peg Test (9-HPT), which is a timed task in which the subject attempts to first place then remove each of 9 pegs from a pegboard using only one hand (Beebe and Lang, 2009). In keeping with standard scoring practices, raw scores for the hand function domain of the SIS were transformed to adjust for the lowest possible raw score and the possible raw score range. Scores for the ARAT were reported as the total points scored when using the impaired hand, and scores for 9-HPT were taken as an average of two timed trials using the impaired hand. At each of the visits for neuropsychological evaluation, anatomical and functional MRI scans were also obtained for each subject.

INTERVENTION

All subjects were administered at least 9 and up to 15 two-hour sessions of interventional BCI therapy using SmartFES, a closed-loop neurofeedback device incorporating multi-modal feedback triggered by EEG. This multi-modal feedback included visual feedback, functional electrical stimulation (FES), and tongue stimulation (TS). A diagram of the device and the sequential stages of each interventional therapy session are provided in **Figure 2**. A detailed description of the procedures followed during each session is provided in the supplementary methods. These sessions took place over a period of up to 6 weeks with two to three therapy sessions per week.

fMRI PARADIGM

Subjects performed a block-design sequential finger tapping task during fMRI scans that consisted of alternating 20-s blocks of tapping vs. rest. Subjects were cued to rest or to tap the fingers of one hand sequentially on a button box, using either visual or tactile (for visually impaired subjects) cues.

Subjects were asked to undergo two fMRI scans using this paradigm—once when tapping with the impaired hand (passive tapping if unable to generate sufficient tappings independently) and again when tapping with the unimpaired hand. Subjects were instructed to hold their heads still throughout the scans, and sufficient padding was provided to discourage head movement.

IMAGE ACQUISITION AND PROCESSING

MRI data was collected on one of two 3 Tesla GE MR750 scanners equipped with high-speed gradients (Sigma GE Healthcare, Milwaukee Wisconsin) using an 8-channel head coil. Padding around the subjects' heads was used to help minimize movements during scans. Functional scans were run using a T2*-weighted gradient-echo echo planar imaging (EPI) pulse sequence sensitive to BOLD contrast. Technical parameters used to acquire these EPI scans are as follows: field of view 224 mm, matrix

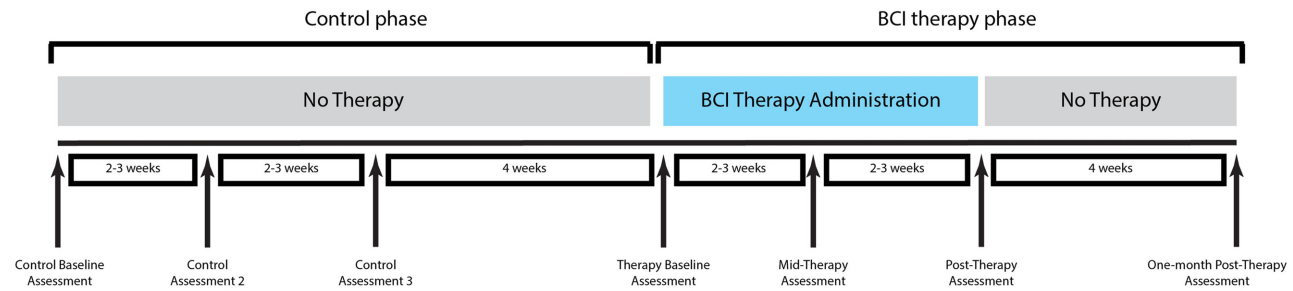

FIGURE 1 | Study paradigm. Functional assessment using Stroke Impact Scale, Action Research Arm Test, Nine-Hole Peg Test, and neuroimaging using fMRI were performed at each assessment.

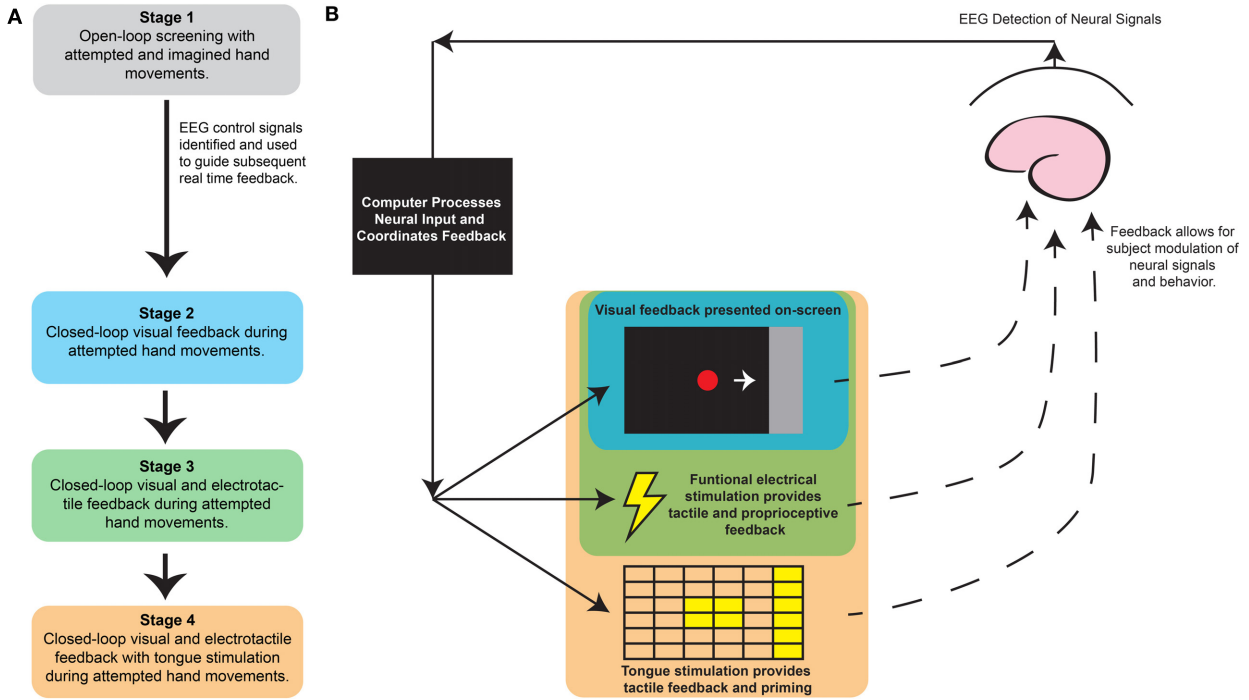

FIGURE 2 | Brain-Computer Interface interventional therapy schematic and session outline. (A) Sequence of BCI interventional therapy session with **(B)** SmartFES device setup with color coding indicating feedback stimuli for the relevant session stages. BCI, Brain-Computer Interface.

64 × 64, TR 2600 ms, TE 22 ms, flip angle 60°, and 40 axial plane slices of 3.5 mm thickness with 3.5 mm spacing between slices. During each fMRI scan, 70 sequential whole-brain acquisitions were recorded. These scanning parameters allowed for complete mapping of the cortex. A T1-weighted high-resolution anatomical image was also obtained for each subject using a BRAVO FSPGR pulse sequence during each MRI scanning session. Technical parameters used to acquire these scans are: field of view 256 mm, matrix 256 × 256, TR 8.16 ms, TE 3.18 ms, flip angle 12°, and 156 axial plane slices of 1 mm thickness with 1 mm spacing between slices.

All pre- and post-processing of MRI data was performed using the AFNI software package (Cox, 1996). The first four volumes of each functional sequence were discarded to allow for signal stabilization. EPI data sets were motion corrected and then spatially smoothed at 6 mm with a full width at half maximum Gaussian kernel. Each voxel timeseries was scaled to a mean of 100, and AFNI's 3dDeconvolve was then used to perform a voxel-wise regression analysis with six motion parameters regressed out. This analysis yielded a voxel-wise t-statistic which was then thresholded based on subsequent analysis as described below. EPI data sets were visually inspected for alignment with anatomical T1 datasets. For cases in which alignment was not acceptable, align_epi_anat.py was used to alight the anatomical T1 scan to the EPI data set in AFNI.

GROUP-LEVEL ACTIVATION ANALYSES

EPI datasets were transformed to 3 × 3 × 3 mm resolution into Talairach space (Talairach and Tournoux, 1988), and AFNI's 3dttest++ was used to generate maps of average group-level activation for each time point. Group-level activation maps were clustered after using AFNI's 3dClustSim to calculate a minimum cluster size of 300 contiguous voxels needed for cluster-based correction for multiple comparisons ($p \leq 0.05$).

For the subjects who had suffered a right-sided stroke with left-sided motor impairment, statistical maps of voxel-wise t-statistics were mirrored about the midline to produce scans demonstrating a stroke lesion in the left brain. These mirrored scans were then used in subsequent group analyses, such that as a group the stroke lesion is evidenced in the left hemisphere and the resulting motor impairment was in the right upper extremity. This process made the assumption that activity in the motor network is symmetric and that these mirrored scans would be otherwise comparable to scans from the subjects with left-sided strokes similar to other studies (Johansen-Berg et al., 2002a; Ward et al., 2003; Darling et al., 2007; Carter et al., 2010a; Confalonieri et al., 2012; Lotze et al., 2012; Stagg et al., 2012).

LI CALCULATIONS AND ANALYSIS

Masks of significant clusters were made for each individual subject performing each task at each timepoint using these minimum clustersize values (range 163–310 contiguous voxels). These masks of significant clusters were created in subject space using the original subject-space voxel-wise maps of t-statistics and also in Talairach space using voxel-wise maps of t-statistics that had been transformed into Talairach space for each scan.

Three sets of ROI masks were created to examine the lateralization of motor function in these subjects to examine changes in laterality not only throughout the brain but also within smaller regions of the brain most relevant to motor function. The first was

a pair of masks designed to capture activity throughout the whole brain (Whole Brain mask). This set was hand drawn in Talairach space to ensure complete coverage of the entire brain and then applied to the Talairached masks of significant clusters of activation for each subject. The second pair of masks (Motor Network mask) was constructed using spheres of radius 6 mm based on regions previously identified as parts of the motor network using an independent component analysis of whole-brain resting state fMRI scans (Shirer et al., 2012). The third pair of masks (Motor Cortex mask) consisted of only the cortical components from the Motor Network mask for each hemisphere. These latter two masks were resampled into subject space and then applied to the masks of significant clusters of activation for each subject. It is worth noting that because the motor network masks were originally based empirically on whole-brain resting state fMRI scans, these masks included areas of both primary and secondary areas of motor cortex and were not completely symmetric in shape. The cerebellum components of each half of the whole-brain and motor network masks were associated with cortical and subcortical structures on the opposite side of the brain because in a normal brain coordinated movement of a given hand is mediated by the contralateral brain hemisphere in conjunction with the ipsilateral cerebellum relative to the hand. A summary of the components of each mask is presented in **Table S3**.

LI was calculated for each fMRI scan using each of these three sets of masks at each of two thresholds to give a quantitative measure of finger tapping lateralization. The formula $(V_I-V_C)/(V_I+V_C)$ was used to calculate each LI value, where V_I is the number of voxels in the ipsilesional hemisphere mask that show significant activation at a preset statistical threshold and V_C is the number of voxels in the contralesional hemisphere mask. Using this system, LI values above 0.2 are considered to represent ipsilesionally lateralized activity, those below −0.2 represent contralesionally lateralized activity, and those between −0.2 and 0.2 correspond to bilateral activity (Springer et al., 1999). Since LI values may change slightly when evaluated at different thresholds of significance (Pillai and Zaca, 2011), each mask was applied at the thresholds of $t = 2.003$ and $t = 4$ (which correspond to $p < 0.05$ and $p < 0.0001$ respectively) in order to evaluate potential trends at both a minimally stringent and a very stringent level of significance.

For subjects who had suffered a right-sided stroke with left-sided motor impairment, ROI masks were applied to individual masks of significant clusters without mirroring about the midline. LI analysis was performed using the formulas detailed above, with higher LI values corresponding to increasingly ipsilesional lateralization of finger tapping function. This process again made the assumption that activity in the motor network is symmetric.

A linear mixed-effects model was used to analyze raw LI values for each mask-threshold combination within data sets from the BCI therapy and control phases to assess for changes at each time point relative to baseline.

LI-BEHAVIORAL CORRELATION ANALYSIS

At the individual level, values for change from baseline LI during finger tapping of the impaired hand were calculated at each time point. Values for change from baseline ARAT, baseline normalized SIS Hand Function domain, and baseline 9-HPT scores were also calculated at each time point for each subject able to complete each respective assessment. Data from subjects who exhibited floor or ceiling effects on a particular measure were not included in the LI-behavioral correlation analysis for that measure. Floor effects were noted when a subject was consistently unable to perform all tasks necessary to complete the assessment at all time points or when the minimum possible score was achieved for the assessment at each of the four time points within a given phase of the study. Ceiling effects were noted when a subject scored the maximum possible points at each of the four time points. Thus, instances of floor and ceiling effects captured zero functional change in the subject using a particular assessment over time. These changes in functional measures were then assessed for correlations with changes in LI using a Spearman's rank correlation analysis, making the assumption of independence among data points. However, because these data were collected using a repeated measures experimental design, some data points are not truly independent of one another. Therefore, relationships found to be statistically significant using the Spearman's rank correlation analysis were then re-analyzed using generalized estimating equations in order to further examine and validate the conclusions of the initial correlation model. Generalized estimating equations provide a method for examining the relationship between two variables that, unlike Spearman correlation analysis, does account for the repeated measures aspect of the data collected but also require the assumption that independent and dependent variables be named explicitly in the model design. All statistical analyses were performed in R statistical software version 3.0.1, which is freely downloadable at http://www.r-project.org/.

RESULTS

PARTICIPANT CHARACTERISTICS

At the time of this analysis, 11 subjects meeting inclusion and exclusion criteria had begun participation in this ongoing study. Among these participants, five were randomized to the BCI therapy group and had completed the BCI therapy phase, three had been assigned to the crossover control group and had completed both control and intervention phases, and data from three additional subjects that had been randomized to the crossover control group was available from the control phase of the study but not from the BCI therapy phase. Therefore, data used in this study represents information obtained from 11 individual subjects with control phase data available for six subjects and BCI therapy phase data available for eight subjects.

Participant characteristics are summarized in **Table 1**. Data from the experimental BCI therapy group comprised data from the BCI therapy phase of the experiment from subjects 1 to 8, while control group data comprised data from the control phase of the experiment from subjects 6 to 11. Among subjects who received BCI therapy, average age was 63 years ($SD = 9.5$ years), and average time from stroke onset was 13.13 months ($SD =$ 8.44 months). More subjects had right-sided impairments than left-sided impairments, but this difference was not significant ($p = 0.14$). More subjects also had cortical strokes than non-cortical strokes, and more subjects were male than female; these differences were not significant ($p = 0.36$ for both comparisons).

Table 1 | Participant Characteristics.

Subject ID	Sex (M/F)	Age (years)	Handedness	Stroke location	Impaired hand	NIHSS (score)	Level of impairment	Time from stroke (months)
1	M	52	R	L MCA	R	8	Severe	15
2	F	61	R	L frontal lobe	R	8	Severe	16
3	M	68	R	L centrum semiovale	R	0	Mild	3
4	M	66	R	L MCA	R	6	Severe	23
5	F	73	R	L MCA	R	0	Mild	2
6	F	75	R	R putamen	L	7	Severe	23
7	M	61	R	L basal ganglia	R	0	Mild	17
8	M	48	L	R pons	L	3	Moderate	6
9	M	56	R	L MCA	R	2	Moderate	11
10	M	48	R	R medulla	L	6	Severe	5
11	M	51	R	R MCA	L	4	Severe	16

L, left; R, right; MCA, Middle cerebral artery.

Among subjects from whom data was collected during from the control phase, average age was 56.5 years ($SD = 10.34$ years), and average time from stroke was 13 months ($SD = 6.96$ months). More subjects who completed the control phase of the experiment had left-sided impairments than right-sided impairments, and more had non-cortical stroke than cortical strokes, but these differences were not significant ($p = 0.688$ for both). Similar to subjects who received BCI therapy, more subjects were male than female, but this difference was not significant ($p = 0.22$). In both groups, more subjects were right-handed than left-handed, but this difference was again not significant ($p = 0.14$ for BCI therapy recipients; $p = 0.22$ among control phase subjects).

SUBJECT RETENTION AND COMPLIANCE

Of the subjects enrolled, there were no drop outs due to subject desire to cease participation in the study or from any reported unpleasant experiences with the assessments or therapies administered. One participant, Subject 7, was not assessed or scanned at the final time point 1 month after the cessation of all BCI therapy due to scheduling conflicts between subject availability and scanner availability that prevented him from participating during the appropriate time window.

FUNCTIONAL ACTIVATION MAPS

Group-level activation maps during finger tapping of the unimpaired hand (**Figure 3**) showed changes in overall activation patterns, with baseline bilateral activation progressing to largely contralesionally lateralized activation over the course of therapy. These changes appear to have persisted to some degree 1 month after the cessation of BCI therapy. When considering group-level activation patterns observed during finger tapping of the impaired hand (**Figure 4**), a progression from more ipsilesional activity at baseline to bilateral activation was observed over the course of therapy. These changes again persisted 1 month after the cessation of BCI therapy. No such trends in group-level activation during finger tapping were noted over the course of the control phase of the experiment among subjects who completed the control phase of therapy.

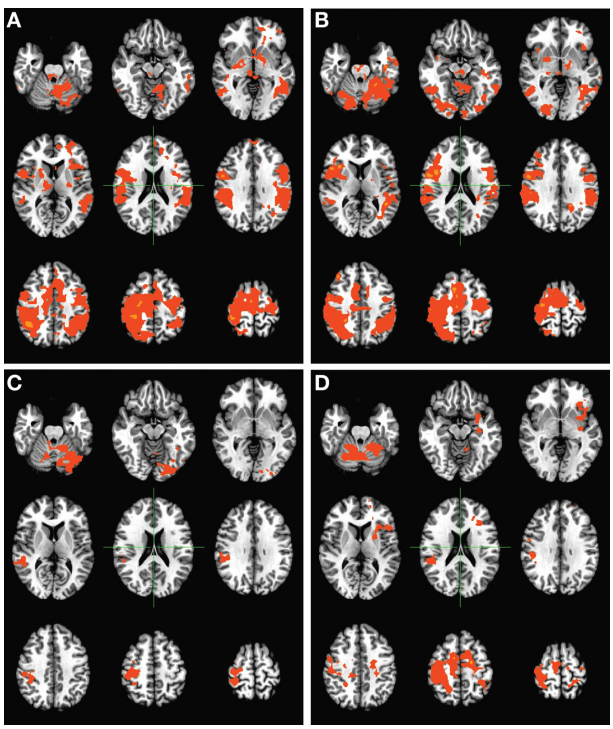

FIGURE 3 | Group level activation maps for finger tapping of the unimpaired hand during the BCI therapy phase of the experiment. Panels demonstrate activation assessed **(A)** pre-therapy, **(B)** mid-therapy, **(C)** upon completion of therapy, and **(D)** 1 month after the cessation of all therapy, and show the development of a lateralized, focal pattern of activation with the administration of therapy. Maps are displayed according to radiological conventions, such that the right side of the image corresponds to the left hemisphere of the brain.

GROUP-LEVEL LI MEASURES

Averaged LI values calculated using each set of ROI masks at each threshold during finger tapping of the unimpaired hand and during finger tapping of the impaired hand showed overall

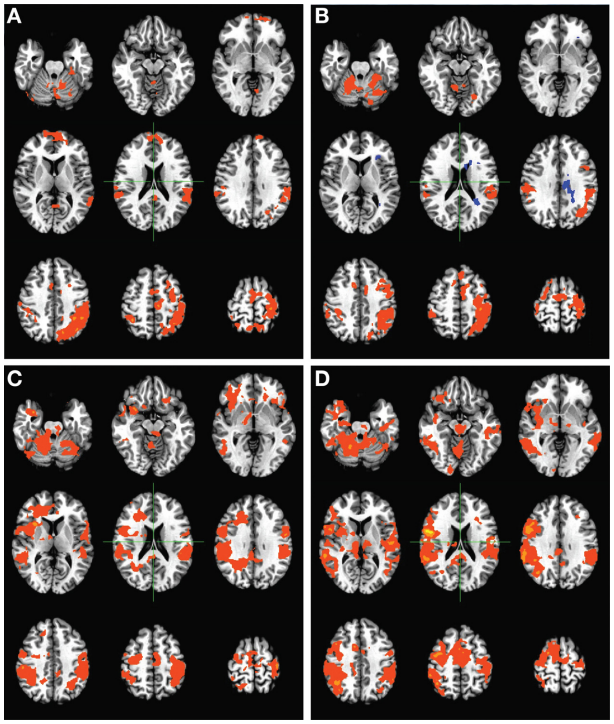

FIGURE 4 | Group level activation maps for finger tapping of the impaired hand during the BCI therapy phase of the experiment. Panels demonstrate activations assessed **(A)** pre-therapy, **(B)** mid-therapy, **(C)** upon completion of therapy, and **(D)** 1 month after the cessation of all therapy, and show the development of a bilateral pattern of activation with increased recruitment of contralesional areas with the administration of therapy. Maps are displayed according to radiological conventions, such that the right side of the image corresponds to the left hemisphere of the brain.

decreases in LI associated with administration of BCI therapy (**Figure 5**). This decrease resulted in an average shift from ipsilesionally lateralized activity at baseline to bilateral activity at all subsequent time points in 4 of 6 mask-threshold combinations during tapping of the impaired hand and a shift from average bilateral activity at baseline to contralaterally lateralized activity in all mask-threshold combinations mid-therapy that persisted after therapy in 5 of 6 mask-threshold combinations during tapping of the unimpaired hand. Analysis of these trends using linear mixed effects modeling revealed these LI decreases to be significantly different from baseline when using the Motor Network and Motor Cortex masks for LI calculations during unimpaired tapping and when using the Whole Brain mask to calculate LI during impaired tapping, as demonstrated by the black stars and plus symbols in **Figure 5**. These trends in LI changes with BCI therapy persisted even when only subjects in the chronic (at least 6 months from stroke onset) stage of stroke were analyzed (blue symbols in **Figure 5**). A similar analysis of LI values from the control phase of the experiment showed no similar trends and no significant changes from baseline at any time point for any of the six mask-threshold combinations.

FUNCTIONAL ASSESSMENT SCORES

Behavioral results for each subject at each time point are provided in the **Tables S1**, **S2**. Floor effects were observed during both the control (Subject 6 ARAT and 9-HPT, Subject 10 SIS Hand Function and 9-HPT, Subjects 8 and 11 9-HPT) and BCI therapy phases (Subject 1 SIS Hand Function and 9-HPT, Subject 2 all assessments, Subjects 4, 6, and 8 9-HPT) of the experiment. Subjects 1, 2, 4, 6, 8, 10, and 11 were unable to complete the 9-HPT task throughout the entire experiment and were therefore considered to be exhibiting a floor effect for this measure. These subjects were not included in subsequent analyses using data from the 9-HPT task. Ceiling effects were observed only during the BCI therapy phase of the experiment (Subject 3 ARAT). At the group level, the Sign test for paired samples was used to compare scores from each of the three behavioral measures mid-therapy, post-therapy, and 1 month after the end of therapy with baseline scores from the BCI therapy phase of the experiment and to compare scores from each assessment during the control phase with baseline control phase values. Changes in these scores were not significantly different from baseline at any time point, even when data from subjects exhibiting floor and ceiling effects were excluded from the comparison.

LI-BEHAVIORAL CORRELATION ANALYSES

A summary of the relationships observed between individual changes in LI and individual changes in behavioral measures during the BCI therapy phase of the experiment is provided in **Table 2**. Of the LI-behavioral relationships from the BCI therapy phase identified as significant at the $p \leq 0.05$ level with the Spearman's approach, two remained significant when re-analyzed with GEE ($p < 0.001$ for both). Among LI-behavioral relationships examined from data obtained during the control phase of the experiment, only the relationship between changes in LI using the Whole Brain mask set at threshold $t = 4$ and changes in ARAT scores was found to be significant using Spearman's rank correlation analysis ($p = 0.039$), although this relationship did not survive when re-analyzed using GEE ($p = 0.647$).

The correlations found to be significant using Spearman's rank correlation analysis that remained significant upon secondary analysis using generalized estimating equations are shown in **Figure 6**.

It is also notable that the calculated estimates for Spearman's rho (**Table 2**) are consistent in sign among correlation analyses performed for the same functional measure (i.e., changes in ARAT and SIS Hand Function scores were all estimated to be negatively correlated with changes in LI, while changes in 9-HPT times were all estimated to be positively correlated with changes in LI). Furthermore, while the direction of the correlations is switched for the 9-HPT measure relative to the other two measures, it is important to interpret this difference while keeping in mind the scoring methods for each. In particular, ARAT and SIS Hand Function are scored positively, with improvements in performance reflected in higher scores, while the 9-HPT scores are reported as the time needed to complete the task in seconds, with improvements in (i.e., faster) performance reflected in lower times. Thus, all estimated Spearman correlations using data from the BCI therapy phase of the experiment were actually consistent

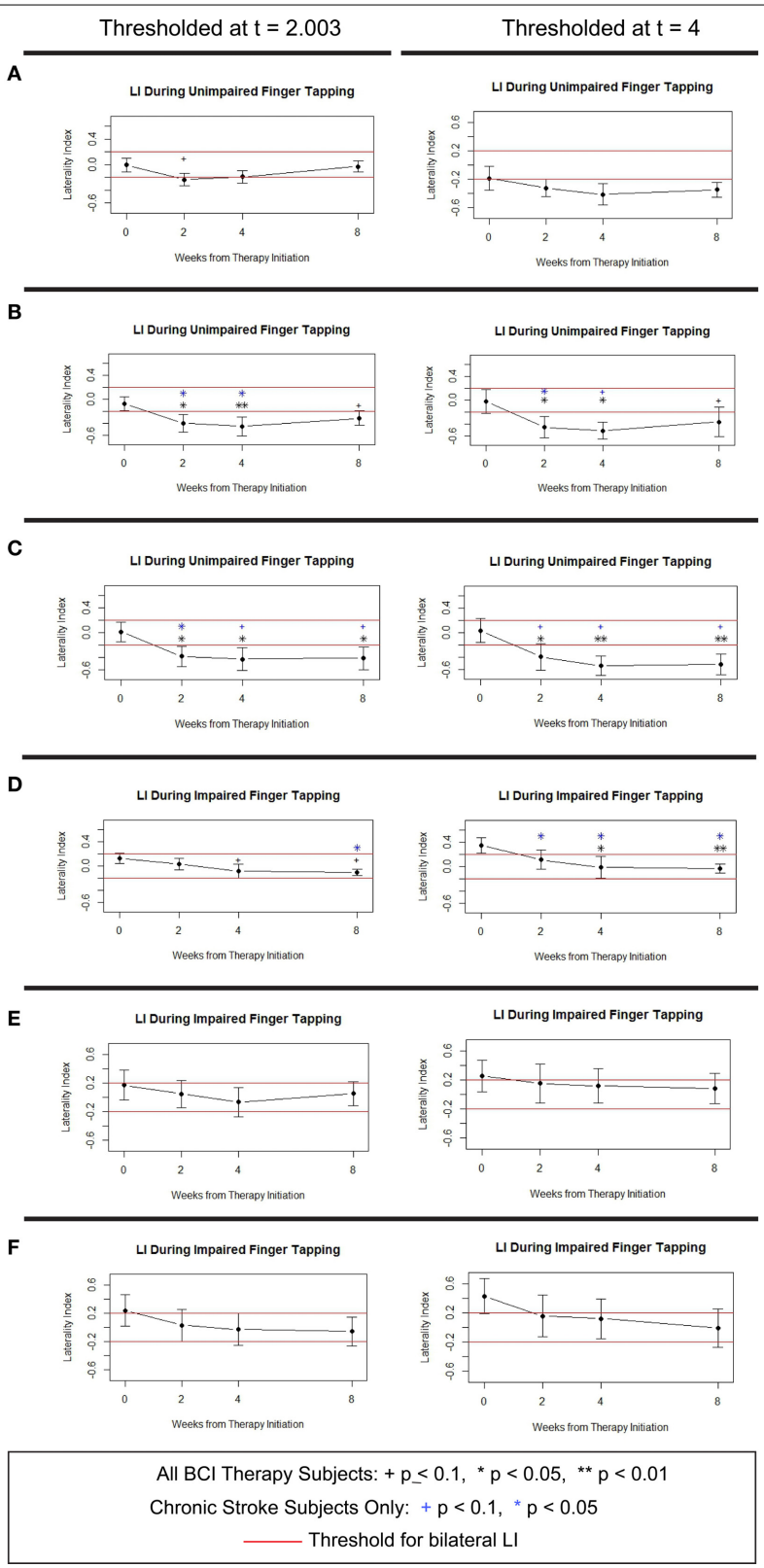

FIGURE 5 | Average LI values over time during unimpaired and impaired tapping from 8 subjects who received BCI therapy. Values were calculated using **(A,D)** Whole Brain mask set, **(B,E)** Motor Network mask set, and **(C,F)** Motor Cortex mask set. Error bars shown are ±1 standard error of the mean. $^{+}0.05 \leq p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$. Symbols in black show significant change from baseline for all 8 subjects who received BCI therapy. Symbols in blue indicate time points for significant change from baseline among the 6 subjects in the chronic stage of stroke who received BCI therapy. LI, Laterality Index.

Table 2 | Correlation analyses between LI changes and functional changes during the BCI therapy phase of the study.

Functional measure	Mask set	Threshold (t)	Spearman's rho	*p*-value
ARAT	Whole brain	2.003	−0.5751	*0.025
ARAT	Whole brain	4.000	−0.3773	0.166
ARAT	Motor network	2.003	−0.315	0.253
ARAT	Motor network	4.000	−0.3556	0.193
ARAT	Motor cortex	2.003	−0.4945	+0.061
ARAT	Motor cortex	4.000	−0.6031	*0.017
SISHF	Whole brain	2.003	−0.3203	0.226
SISHF	Whole brain	4.000	−0.5634	#*0.023
SISHF	Motor network	2.003	−0.2734	0.305
SISHF	Motor network	4.000	−0.3967	0.143
SISHF	Motor cortex	2.003	−0.2493	0.352
SISHF	Motor cortex	4.000	−0.3333	0.225
9-HPT	Whole brain	2.003	0.4444	0.171
9-HPT	Whole brain	4.000	0.3241	0.331
9-HPT	Motor network	2.003	0.2315	0.493
9-HPT	Motor network	4.000	0.205	0.57
9-HPT	Motor cortex	2.003	0.6296	#*0.038
9-HPT	Motor cortex	4.000	0.1429	0.694

**Significant at $p < 0.05$; +trend toward significance at $0.05 < p < 0.1$; #also significant with generalized estimating equations approach.*

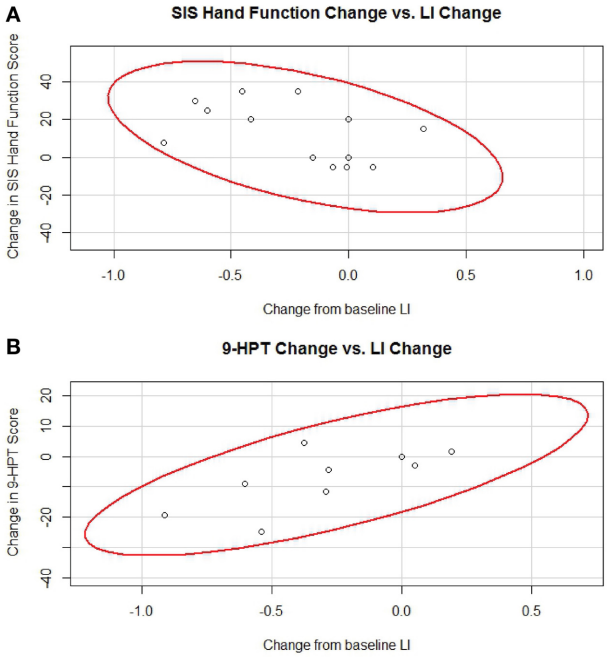

FIGURE 6 | Significant correlations between changes in LI and changes in behavioral measures. (A) Relationship between individual changes in LI and individual changes in SIS Hand Function. Data from 4 subjects representing 15 data points assessed. **(B)** Relationship between individual changes in LI and individual changes in 9-HPT. Data from 3 subjects representing 11 data points assessed. Red lines represent data ellipses at the 95% confidence level. LI, Laterality Index; SIS, Stroke Impact Scale; 9-HPT, Nine-Hole Peg Test.

with an association between decreases in LI and gains in behavioral measures. In contrast, this consistency was not noted in correlation analyses examining potential relationships between changes in LI values and changes in functional measures assessed during the control phase of the experiment.

DISCUSSION

The findings in this preliminary report on the neuroplastic effects of BCI therapy when applied to stroke rehabilitation show changes in task-related brain activation induced by interventional rehabilitative therapy using a closed-loop neurofeedback BCI device. Specifically, group-level changes in the patterns of brain activation associated with finger tapping of each hand were observed with the administration of BCI therapy, with tapping of the impaired hand producing a more bilateral activity pattern post-therapy and with tapping of the unimpaired hand eliciting more lateralized activity involving the hemisphere contralateral to the unimpaired hand (**Figures 3–4**).

These patterns of change noted in our activation maps were further quantified using LI analyses, which demonstrated shifts in activity with BCI therapy from the ipsilesional hemisphere to greater involvement of the contralesional hemisphere (i.e., to bilateral activity) during tapping of the impaired hand and increased lateralization of activity to the hemisphere contralateral to the unaffected hand (i.e., the contralesional hemisphere) during tapping of the unimpaired hand. These LI changes were observed using multiple sets of brain masks at multiple thresholds and generally persisted even when the two subacute stroke subjects in the sample were removed from the analysis (**Figure 5**). The persistence of these findings among chronic stroke subjects argues against this effect arising from a spontaneous recovery process, as chronic stroke is considered to be a time when little or no spontaneous recovery is expected (Nakayama et al., 1994). Furthermore, no such trends or changes in LI were observed in a similar series of scans obtained during a control period in which no BCI therapy was given. That the subanalysis of chronic stroke patients showed LI changes with BCI therapy further supports the hypothesis that these changes were effected, at least in part, by the BCI therapy in that the absence of such effects in the control data set cannot be attributed to the fact that two fewer subjects were assessed during the control phase compared to the full group who received BCI therapy ($n = 8$) as the two groups (chronic stroke patients who received BCI therapy and subjects who completed the control phase of the experiment) were of equal size ($n = 6$). Therefore, if the lack of results in the control group were due merely to a power issue, no such results should be present in the subanalysis using only the six chronic stroke subjects who received BCI therapy. These preliminary differences suggest that such changes in LI may be induced by administration of the BCI therapy used in this study. The persistence of these LI changes up to 1 month after the conclusion of BCI therapy further suggests the possibility for lasting effects to be achieved with the use of this rehabilitative approach.

Taken together, the changes observed in brain activation patterns and LI values during tapping of the impaired and

unimpaired hands associated with the administration of BCI therapy suggest that there may exist differential patterns of response to the same treatment with interventional BCI therapy between the impaired and unimpaired sides of the motor system. These differential responses may be characterized both in the direction of LI change (increasingly lateralized in the case of unimpaired movement vs. increasingly bilateral in the case of impaired movement) as well as in the time course or dose-response of each, with more time or therapy needed before a significant reorganization effect can be observed in LI during an impaired task relative to that needed to observe a significant reduction in LI during an unimpaired task. This difference in brain organization after stroke and re-organization in response to BCI therapy between the ipsilesional and contralesional hemispheres highlights the importance of examining neural responses to treatments such as BCI therapy in stroke survivors even after these systems have been validated in other populations, as it calls into question the degree to which patterns of brain reorganization demonstrated in early studies using healthy normal subjects or limited to stroke subjects with intact cortical functioning (Caria et al., 2011; Ramos-Murguialday et al., 2013) can be generalized to stroke patients and other populations with significant cortical pathologies.

Changes in LI observed during and after the administration of BCI therapy also correlated to changes in behavior observed during the same time period when using some of the mask-threshold combinations. Of the four correlations found to be significant using Spearman's rank-correlation analysis on this data from the BCI therapy phase of the experiment, two remained significant when reanalyzed using a generalized estimating equations approach. The relationship suggested by both significant and non-significant estimated Spearman's coefficients was also consistent across all mask-threshold combinations, with more bilateral LI values correlating to greater functional gains during tapping of the impaired hand across all three behavioral assessments. In contrast, similar correlation analyses performed on data from the control phase of the experiment found only one significant correlation using Spearman's rank-correlation analysis which did not survive when reanalyzed using generalized estimating equations, and the same consistency among the direction of LI change association with improvements in behavioral measures was not observed. The finding of only some mask-threshold combinations and not others giving rise to significant relationships with the behavioral assessments may be due to limitations of the small sample size used, rendering the current preliminary analysis underpowered to detect more subtle relationships between LI changes and functional gains. It is also possible that some mask/threshold combinations are better suited to capturing brain-behavior relationships depending on the behavioral assessment used.

While overall changes in behavioral outcomes during the period of BCI therapy administration were not found to be statistically significant at the group level, the correlations revealed by analyses of individual LI and functional changes suggest the presence of or potential for some degree of sub-clinical functional improvement not well-captured by the assessments used. Indeed, the presence of such correlations between gains in 9-HPT performance and LI changes with BCI therapy further demonstrates the importance of capturing small subclinical gains in function. As only the three least impaired subjects in the group studied who received BCI therapy were able to complete this assessment, changes in 9-HPT performance and LI may show neurological changes that correlate with functional improvement during and after BCI therapy administration and allow us to begin characterizing this relationship present even in highly functioning stroke survivors. It may also be worth noting that while the ARAT and 9-HPT are objective measures of motor function, scores for SIS Hand Function constitute a more subjective measure reliant on self-report. Thus, these changes in brain activity being detected by fMRI may be effecting change both in a subjective measure of how well the subjects believe they are performing, as well as in objective measures of the amount of ability that they are able to demonstrate using standardized motor function tests.

When considering previous work examining correlations between changes in LI and behavioral measures after BCI therapy, one study by Ramos-Murguialday and colleagues found that BCI therapy induced changes in LI of activity in the motor and premotor cortices during attempted movement of the paretic hand, shifting LI toward the ipsilesional hemisphere and correlating the magnitude of these individual shifts with post-therapy motor performance. A similar finding was documented in a case study of a thalamic stroke survivor, in which treatment with BCI therapy was associated with both functional gains and a shift from bilateral brain activation to lateralized activation in the ipsilesional hemisphere (Caria et al., 2011). While the pattern of functional brain reorganization with BCI therapy for stroke rehabilitation documented in these studies appears to describe an LI-behavior correlation opposite that in our findings, it is important to note that these findings by Ramos-Murguialday and Caria were specific to subjects who had suffered subcortical strokes. Thus, these associations may not be generalizable to patients who have suffered cortical damage, as was true of the majority of subjects in the present study. In fact, the pattern of increasingly lateralized LI induced by BCI therapy observed by the Ramos-Murguialday study is similar in pattern and direction to that observed in the unlesioned hemisphere of our subjects during tapping of the unimpaired hand. Our study builds on findings from a feasibility study which indicated that the activity in the brain hemisphere ipsilateral to the affected hand (i.e., the contralesional hemisphere) can be used as control signals for a BCI system designed to respond to movement intention (Bundy et al., 2012) along with the knowledge that in some patients infarction and hypoperfusion may shift areas of activation toward the intact hemisphere in other domains such as language (Prabhakaran et al., 2007). Together, these findings suggest that increased laterality toward the contralateral hemisphere during attempted hand movement may be a typical pattern of response to this type of BCI training in unlesioned cortex.

In designing interventional BCI systems for rehabilitation therapy, such as that used in the present study and in studies referenced previously, there remains a fair amount of uncertainty regarding what patterns of brain reorganization after stroke are optimal in allowing for rehabilitation after stroke and what differences there may be in such patterns among various

subpopulations of stroke survivors. Two of the most prevalent competing theories take different stances regarding whether recruitment or activation of motor areas in the contralesional hemisphere during the chronic stage of stroke is beneficial or detrimental to functional recovery. Each of these views has influenced the development of therapeutic approaches intended to facilitate better rehabilitative outcomes for patients in the subacute and chronic stages of stroke who have reached a functional plateau with traditional standard therapies alone.

Some of these new approaches promote the activation of ipsi- or peri-lesional cortex with or without additionally discouraging activation of contralesional motor areas, effectively encouraging the re-lateralization of functional motor activity to the lesioned hemisphere. These methods stem from observations in studies of spontaneous recovery suggesting that the best recovery outcomes are accompanied by an eventual return to pre-stroke lateralization for these functions. This pattern has been documented in both motor (Turton et al., 1996; Traversa et al., 1997, 1998; Marshall et al., 2000; Calautti et al., 2001; Johansen-Berg et al., 2002b; Richards et al., 2008; Dimyan and Cohen, 2011) and language (Saur et al., 2006; Saur and Hartwigsen, 2012) domains in chronic stroke patients. Additional evidence to support this approach comes from studies of functionally associated neuroplastic change to targeted rehabilitation interventions, which have been shown to correlate with neural plastic changes in the lesioned hemisphere. A systematic review and meta-analysis by Richards and colleagues in 2008 of movement-dependent approaches in stroke recovery including CIMT, task practice, virtual reality training, and bilateral movements also supported this model of ipsilesional lateralization coinciding with better recovery in the sub-acute and chronic phases of stroke (Richards et al., 2008).

In contrast, other approaches have been developed that aim to promote the development of new or secondary pathways in the functional organization of the brain, recruiting areas of the contralesional brain to assist in the motor control of the impaired hand. This theory is based on the fact that 8–10% of corticospinal tract fibers project ipsilaterally in humans and other primates (Galea and Darian-Smith, 1994; Hoyer and Celnik, 2011) with the hypothesis that in some stroke patients, the lesioned hemisphere ceases to inhibit these ipsilateral motor projections which can then be used for control of the impaired arm (Stoeckel and Binkofski, 2010). There is some empirical evidence strengthening the case for attempting to maximize ipsilateral control of a paretic limb, with stroke survivors showing reductions in recovered motor performance after TMS of the contralesional hemisphere (Lotze et al., 2006) and one small study of showing contralesional activation increased with CIMT (Kopp et al., 1999). Motor performance has also been found to correlate more strongly with interhemispheric than ipsilesional functional connectivity following stroke (Carter et al., 2010a). Such studies support the idea that stroke recovery relies at least in part on the functional coordination and activation of the contralesional brain. It has been shown that motor performance in the chronic stage of stroke can be related in particular to the degree of corticospinal tract damage sustained by stroke patients (Stinear et al., 2007), suggesting that this tract plays an integral part in motor recovery. For those who are severely impaired due to a greater burden of irreversible corticospinal tract damage, the recruitment of additional cortical areas may be necessary (Newton et al., 2006; Jayaram and Stinear, 2008), including alternate contralesional pathways, for maximal recovery of motor control. Even with the inclusion of mildly impaired stroke patients, the results of the current study appear to support the participation of the unlesioned hemisphere in the neural reorganization after stroke, which may facilitate recovery of function.

It has been shown that cortical activity in both humans and non-human primates reliably encodes a representation of ipsilateral arm movement (Ganguly et al., 2009) and that differential cortical patterns can be reliably detected within a single hemisphere to differentiate movements of the ipsilateral and contralateral hands (Wisneski et al., 2008). Building on this work, new BCI devices have been developed that can be controlled using only ipsilateral neural signals (Bundy et al., 2012). These devices are being studied primarily in severely impaired subjects most likely to benefit from therapies using this type of approach, as individuals in this stroke population are those most likely to experience a motor recovery process that relies more heavily on new or accessory pathways after significant damage to the ipsilesional corticospinal tract (Bundy et al., 2012). It is important to note that the targeting of these new BCI devices promoting ipsilateral control of the impaired arm to severely impaired stroke survivors, while theoretically motivated, does not necessarily mean that others with less severe impairments could not also benefit from such therapies. Currently, there remains insufficient evidence to determine definitively which of these newer therapies are best suited to stroke survivors with different levels of impairment.

It is also important to remember that the conclusions regarding optimal patterns of functional brain reorganization from the study of one therapy modality may not be generalizable to other therapy modalities such as BCI. For example, two studies following similar populations of chronic stroke patients (all but one with subcortical lesions) found motor function gains to be associated with increased ipsilesional activation laterality or with increased contralesional recruitment during motor tasks of the affected hand after using BCI and gesture therapy respectively (Orihuela-Espina et al., 2013; Ramos-Murguialday et al., 2013). With this in mind, it may not be necessary to identify an optimal pattern of change common across therapy modalities as long as respective approaches are able to induce neuroplastic change and maximize functional recovery in chronic stroke patients. Understanding these patterns of neuroplastic change might then serve simply to allow for optimization within the application of a particular modality.

Although our study had a small and somewhat heterogenous sample of stroke survivors both in terms of motor impairment (mild to severe) and chronicity of stroke (subacute to chronic), BCI induced consistent brain changes along with significant brain-behavioral associative changes in these patients over time that were not observed during a control period in which no BCI therapy was administered. Changes in neural activation patterns were observed with BCI therapy in both primary and secondary motor areas in this population of stroke patients, and these activation patterns were then quantified in LI calculations using masks that included regions of both primary and secondary motor areas.

It is promising that these findings persisted across multiple mask sets at multiple thresholds, some of which were found to have significant correlations to changes in behavioral measures when using both correlation and GEE models. Although the findings in this study are based on a small group of subjects, a subanalysis of only the chronic stroke patients who received BCI therapy showed consistent effects, supporting the hypothesis that administration of this BCI therapy helped to produce the effects observed. The lack of changes in the control group also argues against attributing the effects observed to spontaneous recovery, as the control group was similar to the group that received BCI therapy in numerous measures such as age, sex, handedness, and chronicity of stroke (**Table 1**).

Even though these preliminary analyses were potentially underpowered for the detection of smaller changes in LI earlier in the therapy time course and for the more consistent detection of significant relationships between LI change and behavioral gains, future studies incorporating a larger sample of stroke patients will be able to better characterize these patterns of LI change with BCI therapy and to detect more subtle relationships that these LI changes may have with concurrent behavioral gains. Larger sample sizes will also allow for the investigation of potential cross over effects into domains not directly targeted by the BCI device, such as strength, participation, and activities of daily living, as such effects are expected to be more subtle than those observed in the targeted domain of upper extremity motor function. The use of additional assessments such as the Fugl–Meyer and Chedoke Arm and Hand Inventory may also allow for the detection of more subtle changes in functional capability that may accompany this type of therapy such that floor effects and ceiling effects might be a smaller limitation of future studies. Similarly, future studies on the effects of BCI therapy for stroke rehabilitation will be needed not only to characterize more subtle patterns of neuroplastic change that may result from this type of treatment but also to determine the optimal mask and threshold parameters that might allow LI to be used as an imaging biomarker to assess and track recovery in individuals receiving this type of therapy.

The findings of this study may provide further insight into what theoretical approaches might be optimal in designing future neurofeedback devices and paradigms for motor recovery after stroke, particularly with regard to which patterns of brain activity might be actively rewarded or discouraged by future systems in order to elicit the greatest possible recovery in these patients. In determining whether increased ipsilesional lateralization vs. increased bilateral recruitment is optimal for motor recovery, a review by Dimyan and Cohen documented the former pattern as associated with spontaneous recovery while a small number of interventional and disruptive studies supported the latter in the development of novel interventions to promote neural reorganization in poststroke rehabilitation (Dimyan and Cohen, 2011). This is consistent with the possibility that there exist multiple patterns of neural reorganization that facilitate better recovery after stroke and that such patterns may be modulated with the administration of interventional therapy using newer technologies that are different from those evidenced during spontaneous recovery.

In exploring optimal device design, it may be more important with developing BCI therapies than with the development of other therapy modalities to determine what pattern of neural activity corresponds to the greatest behavioral gains because the BCI system can be programmed to preferentially reward predefined neural signatures. If such patterns for maximal rehabilitation are discovered, it is not difficult to envision the development and clinical use of customized BCI therapy interventions based on the functional and neurological profile of an individual patient, a form of what have been previously termed as "prescriptive" interventions (Carter et al., 2010b).

As the field of interventional rehabilitative therapy using BCI continues to develop, there remains a need for larger studies incorporating an element of randomized control to better understand and characterize the effects being elicited by the BCI therapy itself and also to identify subpopulations of stroke survivors with differential responses to this type of therapy. Ideally, such studies will also incorporate a wide range of behavioral assessments, neuroimaging measures, and connectivity analyses to capture and provide a comprehensive understanding of the various brain and behavior changes induced by BCI therapy and the relations between them.

AUTHOR CONTRIBUTIONS

Brittany M. Young assisted in subject recruitment, data collection, data analysis, and writing. Zack Nigogosyan assisted with data collection, data analysis, and writing. Léo M. Walton assisted with data collection and writing. Jie Song assisted with subject recruitment and data collection. Veena A. Nair assisted with subject recruitment, data collection, data analysis, and writing. Scott W. Grogan assisted with data collection. Mitchell E. Tyler provided TDU hardware and expertise. Dorothy F. Edwards assisted with study design and outcome measure selection and interpretation. Kristin Caldera assisted with subject referral and recruitment. Justin A. Sattin assisted with study design and subject recruitment. Justin C. Williams is one of two lead PI's on this project and supervised the technical and engineering aspects of the work. Vivek Prabhakaran is one of two lead PI's on this project and supervised the neuroimaging aspects of this work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fneng.2014.00026/abstract

Table S1 | Functional outcomes as assessed by SIS Hand Function, Action Research Arm Test, and Nine-Hole Peg Test during the BCI Therapy phase of the experiment. Subjects who were unsuccessful at completing the 9-HPT within 5 min were noted as unable to perform this assessment. Subject numbers in this table match those in **Table 1**, which provides participant characteristics. SIS, Stroke Impact Scale; ARAT, Action Research Arm Test; 9-HPT, Nine-Hole Peg Test.

Table S2 | Functional outcomes as assessed by SIS Hand Function, Action Research Arm Test, and Nine-Hole Peg Test among Subjects completing assessments during the control phase of the experiment. Subjects who were unsuccessful at completing the 9-HPT within 5 min were noted as unable to perform this assessment. Subject numbers in this table match those in **Table 1**, which provides participant characteristics. SIS, Stroke Impact Scale; ARAT, Action Research Arm Test; 9-HPT, Nine-Hole Peg Test.

Table S3 | Components of masks used for LI calculations. Mask regions with "motor and premotor cortex" included components of the precentral, postcentral, middle frontal, medial frontal, and superior frontal gyri. LI, Laterality Index.

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Changes in functional connectivity correlate with behavioral gains in stroke patients after therapy using a brain-computer interface device

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Brain-computer interface (BCI) technology is being incorporated into new stroke rehabilitation devices, but little is known about brain changes associated with its use. We collected anatomical and functional MRI of nine stroke patients with persistent upper extremity motor impairment before, during, and after therapy using a BCI system. Subjects were asked to perform finger tapping of the impaired hand during fMRI. Action Research Arm Test (ARAT), 9-Hole Peg Test (9-HPT), and Stroke Impact Scale (SIS) domains of Hand Function (HF) and Activities of Daily Living (ADL) were also assessed. Group-level analyses examined changes in whole-brain task-based functional connectivity (FC) to seed regions in the motor network observed during and after BCI therapy. Whole-brain FC analyses seeded in each thalamus showed FC increases from baseline at mid-therapy and post-therapy ($p < 0.05$). Changes in FC between seeds at both the network and the connection levels were examined for correlations with changes in behavioral measures. Average motor network FC was increased post-therapy, and changes in average network FC correlated ($p < 0.05$) with changes in performance on ARAT ($R^2 = 0.21$), 9-HPT ($R^2 = 0.41$), SIS HF ($R^2 = 0.27$), and SIS ADL ($R^2 = 0.40$). Multiple individual connections within the motor network were found to correlate in change from baseline with changes in behavioral measures. Many of these connections involved the thalamus, with change in each of four behavioral measures significantly correlating with change from baseline FC of at least one thalamic connection. These preliminary results show changes in FC that occur with the administration of rehabilitative therapy using a BCI system. The correlations noted between changes in FC measures and changes in behavioral outcomes indicate that both adaptive and maladaptive changes in FC may develop with this therapy and also suggest a brain-behavior relationship that may be stimulated by the neuromodulatory component of BCI therapy.

Keywords: brain-computer interface, stroke rehabilitation, functional connectivity, BCI therapy, UE motor recovery, fMRI

INTRODUCTION

Decreases in stroke mortality rates began accelerating in the 1970s (Lackland et al., 2014), and reduced stroke mortality was named as one of the 10 great public health achievements in the United States from 2001 to 2010 by the Centers for Disease Control and Prevention (2011). These trends have contributed to a growing population of stroke survivors currently estimated at 4 million individuals in the United States alone (Go et al., 2014). Nevertheless, approximately 795,000 individuals experience a new stroke each year (Go et al., 2014), with up to 50% of survivors suffering from some persistent neurological disability (Kelly-Hayes et al., 2003). Stroke continues to be a leading cause of serious long-term disability, resulting in billions of dollars of economic costs each year (Towfighi and Saver, 2011). Given the magnitude of

such costs and the growing population of stroke survivors, there is a need for a better understanding of the mechanisms that underlie stroke recovery and new methods to facilitate stroke rehabilitation.

Functional connectivity (FC) is a measure of the temporal correlation of activation between spatially separate brain regions. Such activation has been shown to be distributed among neuronal areas via functionally or structurally connected networks of neurons (Biswal et al., 1995; James et al., 2009; Nocchi et al., 2012; Jiang et al., 2013; Varkuti et al., 2013). With regard to stroke rehabilitation, the understanding of the FC changes that result from stroke and those observed during the recovery process is a growing area of interest that may be used to guide future therapeutic approaches (James et al., 2009; Grefkes and Fink, 2011; Westlake and Nagarajan, 2011; Jiang et al., 2013; Varkuti et al., 2013). One study of subcortical stroke survivors has shown reorganization in the ipsilesional motor cortex to be strongly associated with post stroke recovery (Zhang et al., 2014). However, another study of subcortical stroke patients found different patterns of increased resting-state FC in the sensorimotor network in those with right hemisphere strokes compared to those with strokes in the left hemisphere (Wang et al., 2014). Clearly, there is much to be learned in the process of characterizing not only changes in FC observed in stroke patients but also in understanding how these changes may be modulated during recovery facilitated by rehabilitative therapies.

Brain-computer interfaces (BCIs) are systems which use detected neural activity to generate real time feedback and present this feedback to the user whose neural activity is being monitored. The user can then use this feedback to learn how to modulate context-specific brain activity. These technologies are being incorporated into a new class of devices intended to facilitate stroke rehabilitation with some success in small-scale studies (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Liu et al., 2012; Takahashi et al., 2012). A growing number of studies have shown changes in brain activation associated with imaginary and attempted movements of an impaired upper extremity with the use of these devices in rehabilitative applications intended to improve motor function (Broetz et al., 2010; Caria et al., 2011; Ramos-Murguialday et al., 2013). There is evidence that such changes in activation are accompanied by changes in FC to the areas targeted by training with the BCI system (Rota et al., 2011). In one study of stroke patients, gains in resting-state FC observed after rehabilitative therapy using a BCI device also correlated positively with gains in motor outcomes documented during the same period (Varkuti et al., 2013). However, studies of FC changes observed with the administration BCI therapy remain limited. A more complete understanding of FC changes in response to therapies using BCI systems and how these changes may relate to behavioral outcomes is important in understanding the mechanisms that underlie clinical gains that may be elicited with this new class of devices.

The aim of this paper is to identify changes in motor network FC observed with the administration of interventional rehabilitation therapy using a BCI device and to examine how these changes might relate to behavioral outcomes in stroke patients. We hypothesize that FC in the motor network during finger tapping of the impaired hand will increase with the administration of BCI therapy and that these increases will correlate with gains in behavioral measures assessed outside of the scanner.

MATERIALS AND METHODS

PARTICIPANT RECRUITMENT AND CHARACTERISTICS

Thirty patients with persistent upper-extremity motor impairment resulting from ischemic or hemorrhagic stroke were contacted regarding study participation. Of these, 16 expressed interest in participating in our study with nine individuals having completed a full course of BCI therapy and MRI assessments thus far. Exclusion criteria included the presence of neurodegenerative disorder (e.g., dementia), other neurological or psychiatric disorders (e.g., schizophrenia), and the inability to provide informed consent. Subjects were also excluded if they had allergies to electrode gel used during the therapy sessions, if they had undergone treatment for recent infectious diseases, if lesions of the oral mucosa were present, if they were pregnant or likely to become pregnant during the course of the study, or if they were unable to safely and comfortably undergo MRI. Of the nine subjects described in this paper (6M, 3F), the average age was 62 years (SD = 9.2 years). Average time from stroke onset was 12.9 months (SD = 7.9 months). More subjects were right-handed ($N = 7$) than left-handed, and more subjects had right-sided impairments ($N = 7$) than left-sided impairments, but these differences were not significant ($p = 0.18$). This study was approved by the University of Wisconsin Health Sciences Institutional Review Board. All subject provided written informed consent prior to participation.

INTERVENTION SCHEDULE AND BEHAVIORAL ASSESSMENTS

Subjects were assessed no more than 1 week prior to the start of BCI therapy (pre-therapy), at the midpoint of therapy, within 1 week after completion of all BCI therapy (post-therapy), and 1 month after the end of the BCI therapy period. Each assessment involved obtaining both behavioral measures as well as MRI scans. Four of the nine subjects were also administered the behavioral assessment at three additional time points during a pre-therapy monitoring period prior to the administration of any BCI therapy. Behavioral measures administered at each assessment included the Action Research Arm Test (Carroll, 1965; Lang et al., 2006), the 9-Hole Peg Test (9-HPT) (Beebe and Lang, 2009), and the Stroke Impact Scale (SIS; Duncan et al., 1999; Carod-Artal et al., 2008). Scores for the 9-HPT were calculated as the average of two attempts using the impaired hand. ARAT scores reflect a total score assigned for the subject's impaired hand. Of the domains of the SIS, this study focused on the Activities of Daily Living (SIS ADL) and Hand Function (SIS HF) domains, as these represent the domain most closely related to the motor functions practiced with the BCI therapy administered (SIS HF) and the domain most reflective of global function (SIS ADL) that may inform the clinical implications of the results. SIS domain scores were transformed to yield a percentage of possible points obtained, in accordance with standard SIS scoring practice. All SIS domain scores discussed in this paper refer to these transformed scores.

BCI THERAPY AND SESSION SEQUENCE

All subjects received up to 15 2-h sessions of interventional therapy using an EEG-guided BCI device, which incorporated visual display, tongue stimulation, and functional electrical stimulation as feedback. These BCI therapy sessions were scheduled over the course of up to 6 weeks with no more than three sessions per week.

All BCI therapy was set up using BCI2000 software (Schalk et al., 2004) version 2 with in-house modifications to allow for administration of additional tongue stimulation (TDU 01.30, Wicab Inc.) and functional electrical stimulation (LG-7500, LGMedSupply; Arduino 1.0.4). A 16-channel EEG cap and amplifier (Guger Technologies) were used for the detection and recording of all EEG signals during the BCI therapy sessions. Each 2-h session began first with an open-loop screening task used to identify appropriate control signals. During the screening task, the subject was cued to perform attempted movement of either hand alternating with periods of rest using the cues "right", "left", and "rest". The specific movements used varied across subjects, as the specific movements used were individualized to the baseline abilities and recovery goals of each patient. Repeated opening and closing of the hand and wrist extension were common choices among subjects in this study, although some chose to use wrist flexion or squeezing motions. Cues were shown as words on a screen one at a time in blocks of 4 s. Each cue was shown at least 10 times at the beginning of each session. During this screening task, no feedback was provided to the subject. Data collected during these open-loop trials then determined appropriate EEG-based control features to guide all subsequent closed-loop tasks, using a process previously described to determine optimal control features (Wilson et al., 2009).

Attempted movement rather than motor imagery was used for both initial screening and for subsequent closed-loop feedback conditions with the intent of making the training conditions of the neurofeedback task as similar as possible to the mental processes invoked when attempting functional real world movement. This was done because when using the BCI system as an assistive feedback device for rehabilitative therapy to help reestablish function, rather than as an augmentative means of replacing a lost function, it is important for the effects of the training to be accessible to the subject beyond the laboratory environment. Therefore, we based control signals on neural activity patterns generated during attempted movements in an attempt to maximize the extent to which the context-specific strengthening of movement-related patterns of brain activity might persist and benefit the individual when attempting movements beyond the therapy period.

While many BCI systems were originally controlled using motor imagery alone, these early systems were developed using individuals without motor impairments with motor imagery used as a way to establish the ability to control a BCI device independent of the production of normal movements (Leuthardt et al., 2004). Later studies demonstrating the ability of impaired individuals to successfully achieve similar control of BCI devices as seen with healthy subjects continued with the use of motor imagery, recreating similar task conditions to those with which healthy subjects were trained and often relying on paradigms that did not target use of actual deficits present in the impaired populations tested (Wolpaw and Mcfarland, 2004). It may also be important to acknowledge that many early BCI devices were developed to function as augmentative devices rather than for rehabilitative purposes, which may partially explain the heavy emphasis on using mental tasks like motor imagery that could be performed consistently in the absence of any actual movement over mental tasks that might also produce more heterogeneous amounts of physical movements due to variations in the severity of deficits among subjects. Therefore, while these early systems established a precedent of motor imagery as a standard method for training with motor-oriented BCI devices, this tradition does not preclude the ability of an individual to control the device with mental tasks other than motor imagery and even with brain regions anatomically distinct from the sensorimotor cortical areas that are often used (Felton et al., 2007).

BCI devices that rely on motor imagery continue to be used today for both rehabilitative (Buch et al., 2008; Daly et al., 2009; Broetz et al., 2010; Prasad et al., 2010; Caria et al., 2011; Shindo et al., 2011; Varkuti et al., 2013) and augmentative (Kubler et al., 2005) purposes, although newer systems have also incorporated actual movement into their protocols using BCI systems for rehabilitative purposes with some success (Daly et al., 2009; Prasad et al., 2010; Takahashi et al., 2012; Ramos-Murguialday et al., 2013; Mukaino et al., 2014). While therapy using our BCI system encourages actual attempted movements rather than imagined movements during both open-loop and closed-loop conditions, we believe that this system can still be classified as a BCI as the feedback provided by the device is controlled purely by neural signals detected by EEG, creating a real time interface between the brain and the computer-generated stimuli.

Subjects were then taught to perform a closed-loop task during which real time visual feedback was presented to help the subject learn to modulate cortical activity during attempted movement of each hand. This feedback was presented in the context of a game. The subject was instructed to move a cursor onto a target area. Target areas were presented on either the left or right side of the screen, and subjects were instructed to use movement of the left or right hand to move the cursor in the left or right direction respectively. Lateral cursor movement was determined by the subject's real time EEG signals, with cortical activity associated with attempted left (right) hand movement translating to leftward (rightward) movement of the cursor. At each therapy session, subjects first completed a goal of at least 10 runs, each run consisting of 8–12 trials and each trial presenting one of four targets, with visual feedback alone as described.

After approximately 10 trials with visual feedback alone, functional electrical stimulation and tongue stimulation were added to the same game play task. Functional electrical stimulation was applied to the muscles of the impaired arm and triggered such that electrical stimulus was only delivered when appropriate neural activity signals corresponding to attempted movement of the impaired hand were detected on EEG during a trial in which it was necessary to move the cursor toward a target on the impaired side of the body. Tongue stimulation paralleled the spatial information of visual feedback, providing continuous electrotactile stimulation of the tongue on an electrode grid during each trial. Stimulus

delivered in areas of the tongue stimulation grid represented the positions of the cursor and target on screen.

Subjects were allowed to take short breaks between trials if desired or upon request. In order to keep the sessions more interesting, game dynamics (e.g., size of the target) could be changed to make the task more difficult once subjects achieved adequate cursor control and accuracy (approximately 70% of targets attained) at a given level of difficulty. Similarly, if a subject who had previously been advanced to a more difficult level of game play showed a sudden reduction in their ability to control the cursor, the level of difficulty could be reduced temporarily as the subject reattained sufficient control to increase the proportion of targets attained. These adjustments were made to help keep the subject engaged at a task that is consistently challenging enough to minimize boredom but not so challenging that the subject loses motivation.

MRI TASK INSTRUCTIONS

Subjects were scanned during a block-design task fMRI during which they were instructed to alternate finger tapping of the impaired hand with rest in 20 s blocks. Cues to the tap and rest conditions were given using either visual or tactile cues. Subjects unable to generate tapping movements on their own performed assisted tapping during tap blocks. For both functional and anatomical scans, subjects were instructed to lie still and attempt to minimize any head movements.

MRI ACQUISITION AND PROCESSING

All MR images were acquired on one of two GE MR750 3T scanners (GE, Milwaukee, Wisconsin) equipped with high-speed gradients and using an 8-channel head coil. Padding around subjects' heads was used to help minimize movement. Functional scans were obtained using a T2*-weighted gradient-echo echo planar imaging (EPI) pulse sequence sensitive to BOLD contrast: field of view 224 mm, matrix 64 × 64, TR 2600 ms, TE 22 ms, flip angle 60°, acquiring 40 axial plane slices of 3.5 mm thickness with 3.5 mm spacing between slices. In total, 70 sequential whole-brain acquisitions were recorded during each functional scan. A T1-weighted high-resolution anatomical image was also obtained during each scanning session using a BRAVO FSPGR pulse sequence: field of view 256 mm, matrix 256 × 256, TR 8.16 ms, TE 3.18 ms, flip angle 12°, and 156 axial plane slices of 1 mm thickness with 1 mm spacing between slices.

All processing and pre-processing of MR scans was performed using Analysis of Functional NeuroImages (AFNI; Cox, 1996). The first four volumes of each functional scan were removed to allow for signal stabilization. Functional data sets were motion corrected and spatially smoothed at 6 mm with a full width at half maximum Gaussian kernel. Each voxel time-series was scaled to a mean of 100, and six motion parameters were regressed out. EPI data sets were visually inspected for alignment with anatomical T1 datasets, using align_epi_anat.py to align the anatomical T1 scan to the EPI data set if alignment was not acceptable upon first inspection.

Each of seven regions previously identified as components of the motor network (Shirer et al., 2012) was seeded with an ROI of radius 6 mm. Regions were the left thalamus, right thalamus, left primary motor cortex, right primary motor cortex, right supplementary motor area, left cerebellum, and right cerebellum. Whole-brain connectivity analyses to each seed region were conducted using the motion regressed residual time-series derived from the functional scans. Whole-brain connectivity maps were then transformed into a standardized brain space (Talairach and Tournoux, 1988). For the two subjects with right-sided stroke lesions, images were flipped along the mid-sagittal line so that in group-level comparisons the left hemisphere was ipsilesional and the right hemisphere was contralesional.

STATISTICAL ANALYSIS

All statistical analyses were conducted using either AFNI (Cox, 1996) software or in *R* statistical software (version 3.0.1). A paired *t*-test was used to identify areas of significant connectivity change at the group level. Maps were cluster corrected for multiple comparisons, with minimal cluster size 300 voxels, and thresholded at $t \geq 2.366$ ($p < 0.05$). Within-subject correlation matrices for the 21 ($7 \times (7 - 1)/2$) pairs of ROI seeds were computed from motion regressed residual time-series for each subject. The Fisher *Z*-transform was applied to each of these correlation coefficients to produce measures of an approximately normal distribution, and these transformed coefficients were then used in all subsequent analyses.

Average network connectivity was calculated by averaging all 21 transformed correlation coefficients representing functional connections between each pair of seeds in the motor network. Connections were classified as either interhemispheric or intrahemispheric, and these groups were analyzed for differences using linear mixed effects modeling.

Changes from pre-therapy baseline in correlation strength between each pair of seed regions were analyzed for correlation with changes from baseline behavioral measures. This was done first by calculating Pearson's *r* and applying fdr correction to the resulting *p*-values obtained for each correlation examined, making the assumption of independence among data points. Recognizing that these data follow the same individuals at multiple time points and are therefore not truly independent, a follow-up analysis of correlations found to be significant using Pearson's *r* and fdr correction was conducted using generalized estimating equations (GEE), which does account for the repeated measures component of the data collected but requires the assumption that an independent and dependent variable can be named in the model. Subjects that exhibited floor or ceiling effects in behavioral measures were excluded from correlation analyses of that measure.

RESULTS

BEHAVIORAL MEASURES

Group performance on each of the four behavioral measures assessed is summarized in **Table 1**. No significant group differences in behavioral measures were found when comparing mid-therapy, post-therapy, and 1 month post therapy assessment scores with pre-therapy baseline measures in any of the four behavioral outcomes. The average amount of change observed in behavioral measures during the pre-therapy period and

Table 1 | Group averages on each of four behavioral measures at each of four time points.

	ARAT (points)	9-HPT (seconds)	SIS ADL (score)	SIS HF (score)
Pre-therapy	27.78 (9.06)	52.59 (7.89)	68.06 (6.30)	26.11 (9.67)
Mid-therapy	26.44 (8.60)	52.10 (7.53)	72.22 (6.28)	30.56 (10.59)
Post-therapy	28.11 (9.03)	53.13 (6.70)	68.89 (5.59)	28.89 (10.30)
One month after BCI therapy	25.38 (10.09)	41.33 (7.00)	70.31 (6.02)	25.31 (10.74)

Numbers shown are group averages with standard error of the mean in parentheses. Scores for ARAT, SIS ADL, and SIS HF reflect data from all nine subjects. Scores for 9-HPT reflect values of only the four subjects who were able to complete the task within the allotted 5 min. ARAT = Action Research Arm Test, 9-HPT = Nine-Hole Peg Test, SIS ADL = Stroke Impact Scale—Activities of Daily Living, SIS HF = Stroke Impact Scale—Hand Function.

Table 2 | Average change observed during pre-therapy and BCI therapy periods for each of four subjects with additional behavioral assessments prior to the start of BCI therapy.

	ARAT (points)		9-HPT (seconds)		SIS-ADL (score)		SIS-HF (score)	
Subject	**Pre-Therapy**	**BCI Therapy**	**Pre-Therapy**	**BCI Therapy**	**Pre-Therapy**	**BCI Therapy**	**Pre-Therapy**	**BCI Therapy**
A	Floor	Floor	Unable	Unable	−11.67	5	1.67	−5
B	−0.33	2.5	−33.51	−3.49	−2.5	3.75	−1.67	0
C	2.67	10	Unable	Unable	−11.67	2.5	0	26.67
D	2	−4.33	−26.11	17.52	−2.5	−21.67	18.33	−21.67

Floor = a floor effect was observed in which the subject was unable to score points for the measure at any time point assessed. Unable = subject was unable to perform the task within the allotted 5 min time period. ARAT = Action Research Arm Test, 9-HPT = Nine-Hole Peg Test, SIS ADL = Stroke Impact Scale—Activities of Daily Living, SIS HF = Stroke Impact Scale—Hand Function.

during the BCI therapy period for each of the four subjects who completed three additional behavioral assessments prior to the start of BCI therapy is presented in **Table 2**. Changes for these subjects during the pre-therapy period were smaller in magnitude for the ARAT and SIS HF scores. Average change in SIS ADL was negative for all four subjects during the waitlist period, with positive changes noted during the BCI therapy period in three of the four.

BCI PERFORMANCE RESULTS

The average performance accuracy across all subjects for the BCI cursor task for each session is shown in **Figure 1A**. Subjects were able to consistently maintain an average accuracy above 0.5, meaning that on average subjects were able to successfully control the cursor well enough to achieve successful target attainment in over half the trials. This maintenance of greater than 50% overall accuracy throughout the therapy period was accompanied by a general increase in the average Fitts's Index of Difficulty (Fitts, 1954) for each session, as can be seen in **Figure 1B**. The pattern of relatively constant accuracy over sessions along with a general increase in difficulty is consistent with the method of increasing task difficulty at an individualized pace, advancing individual subjects to more difficult game play parameters once they able to increase accuracy on individual runs to approximately 70%. Individually, a binomial test of each subject's performance showed individual accuracies across all completed non-adaptive runs to be significantly greater than chance ($p < 0.05$ for each subject). Due to a computer error, BCI performance data was lost for a small number of runs; however, these lost runs represented less than 4% of all applicable data and were not known to be different from the remaining 96% of runs used in the analysis presented.

fMRI WHOLE-BRAIN CONNECTIVITY ANALYSIS

Maps of significant increases in FC to thalamic seed regions are shown in **Figure 2**. At mid-therapy, increases in FC were noted between the ipsilesional thalamus seed and parts of the bilateral precuneus and bilateral cingulate. Increases were also noted between the contralesional thalamus and the contralesional cerebellum as well as with the bilateral precuneus. Upon completion of BCI therapy, increases were noted between the ipsilesional thalamus and the contralesional cingulate, contralateral paracentral lobule, and the bilateral precuneus. Increases were also noted between the contralesional thalamus and the bilateral anterior cingulate and the ipsilesional superior and middle frontal gyri. Significant group-level changes in FC at mid-therapy and as well as upon completion of therapy were not observed for other seed regions.

NETWORK CONNECTIVITY ANALYSIS

The average connection strength over the entire network was increased from baseline upon completion of BCI therapy, but this increase was not statistically significant. No individual connections within the network showed significant changes from baseline at the group level during the study period.

Analyses of the interhemispheric and intrahemispheric components of the network showed no significant differences between the two types of connections in connection strength or in patterns of change over the study period. As shown in **Figure 3**, the

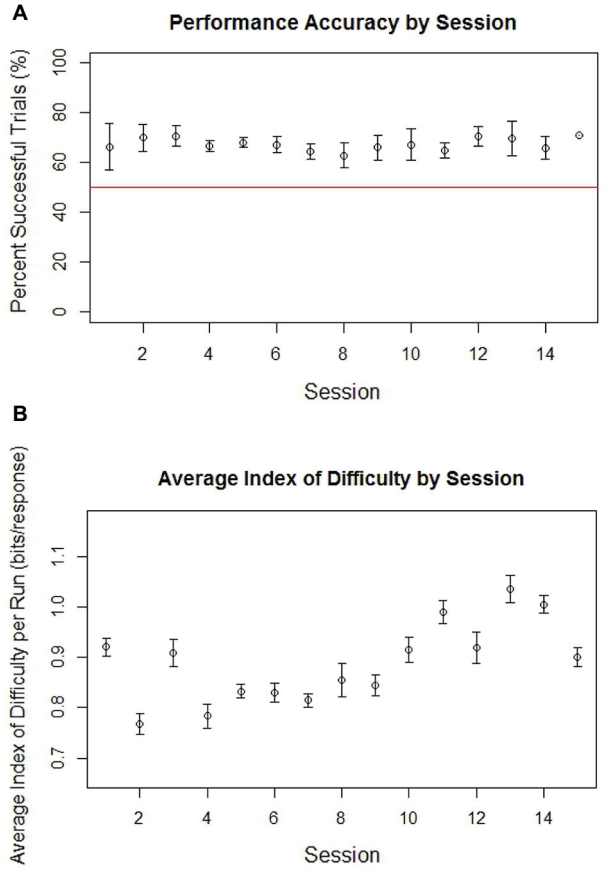

FIGURE 1 | Average accuracy in percent successful trials (A) and average Fitt's Index of Difficulty (B) by run for all non-adaptive runs of BCI cursor task game play across all subjects grouped by session. The red line in the graph of accuracy for each session is drawn at 0.5, which represents the level at which half of trials would be successful. Error bars represent the standard error.

average within-subject interhemispheric connection strength correlated with average within-subject intrahemispheric connection strength using a Pearson's r calculation (R^2 range 0.77–0.95; $p < 0.002$ at all four time points).

BEHAVIORAL CORRELATIONS WITH CHANGES IN MOTOR NETWORK CONNECTIVITY

Changes from pre-therapy baseline in average within-subject network connectivity across the pre-, mid-, post-, and 1 month after-therapy time points correlated to changes in all four behavioral measures using Pearson's r. As shown in **Table 3**, these relationships remained significant using a GEE approach for the 9-HPT (**Figure 4A**), SIS ADL (**Figure 4B**), and SIS HF (**Figure 4C**) measures.

BEHAVIORAL CORRELATIONS WITH CHANGES IN INDIVIDUAL CONNECTION STRENGTHS

A summary of Pearson's correlations found to be significant after fdr correction that also survived GEE analysis between changes in individual connection strength within the motor network and changes in behavioral scores is presented in **Table 4**. At least one connection achieved significance using both methods for each of the four behavioral measures examined. Of these connections, the majority were connections involving either the ipsilesional or contralesional thalamus.

DISCUSSION

The results of these preliminary analyses are suggestive of a relationship between the changes in FC and those in behavioral outcomes observed with the administration of BCI therapy. Although no significant behavioral gains were demonstrated at the group level, behavioral measure changes during the pre-therapy and BCI therapy periods for subjects assessed at additional time points prior to intervention suggest that on the individual level there may still be a differential response to therapy using the BCI system not explained by practice effects on different behavioral tasks. The lack of significant group changes over the course of the therapy period in overall FC at the network and connection levels may be due to the small number of individuals included in these analyses, rendering them underpowered to identify more subtle changes that may have been present.

The thalamus is a component of the motor network (Shirer et al., 2012) that lesion studies in both primates (Bornschlegl and Asanuma, 1987; Canavan et al., 1989) and humans (Lee and Marsden, 1994) have shown to be important for normal motor learning and motor function. In the context of motor recovery after stroke, increases in ipsilesional thalamic activation have been shown to correlate with motor performance in chronic stroke patients undergoing treadmill training (Enzinger et al., 2009), and abnormalities in resting-state FC with the thalamus have been found in stroke patients, with some of these connections found to correlate with motor outcomes (Wang et al., 2010; Park et al., 2011). One longitudinal study of subcortical stroke patients observed changes in FC between the ipsilesional thalamus and contralesional areas that correlated with functional outcomes during the first year following stroke (Wang et al., 2010). Another study focusing on supratentorial stroke patients found increased FC between the ipsilesional motor cortex and the bilateral thalamus compared to healthy controls, with FC between the ipsilesional motor cortex and the contralesional thalamus correlating positively with motor recovery 6 months following stroke (Park et al., 2011).

While the use of an EEG-guided BCI device rewards the modulation of largely cortical neural activity without direct feedback intended to target subcortical activity due to the nature of EEG, the finding of significant changes in FC to each thalamus in these patients indicates that changes in thalamic FC may be encouraged by the brain-driven nature of BCI therapy. These increases may relate to the fact that feedback from the BCI device used in this study is controlled in part by desynchronization of the mu rhythm over the sensorimotor cortex, which is thought to be produced by thalamocortical circuits (Niedermeyer and da Silva, 2005). Furthermore, it is possible that the achievement-based constraints of the BCI-guided task employed in this therapy, which encourages and rewards appropriate cortical activity with the attainment of a target that can be counted or scored, contribute to this effect. The areas observed to have increased FC to the ipsilesional and

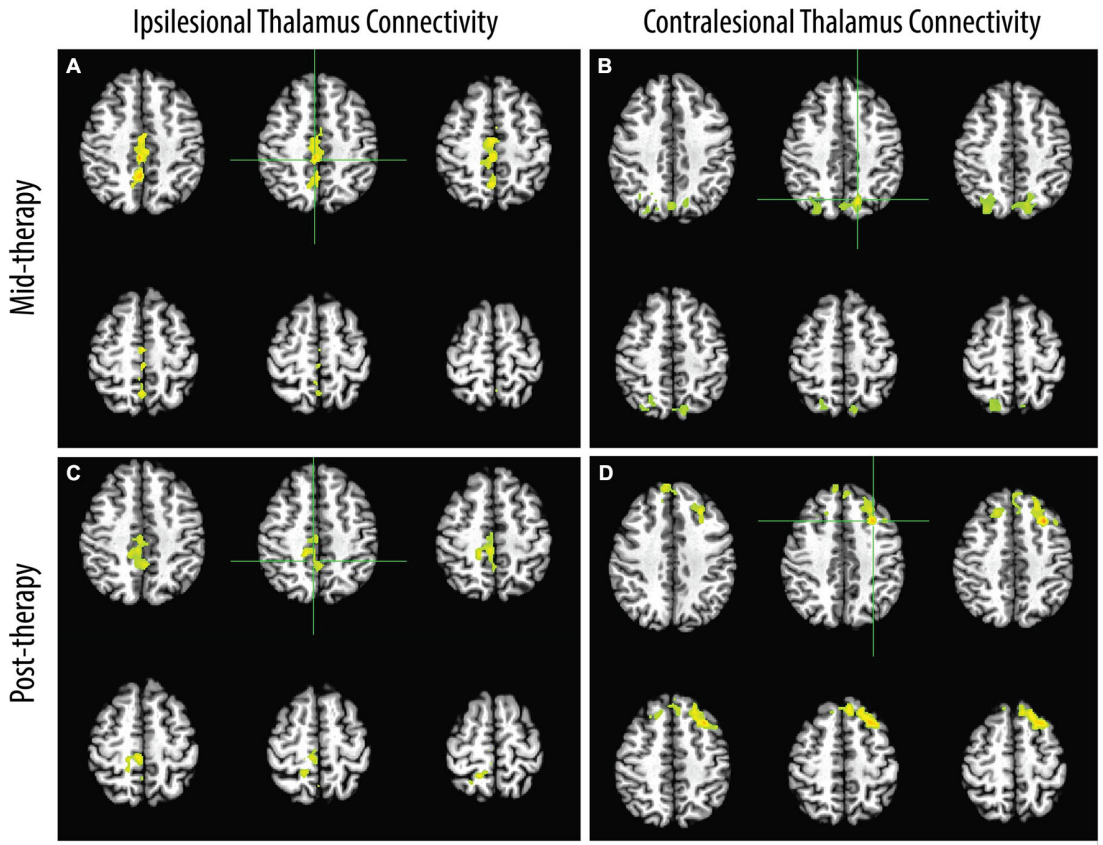

FIGURE 2 | Areas of group-level increases from pre-therapy baseline in FC to seeds in the ipsilesional (A, C) and contralesional (B, D) thalami observed mid-therapy and upon completion of therapy. Hemispheres shown on the right side in the image correspond to the ipsilesional hemisphere.

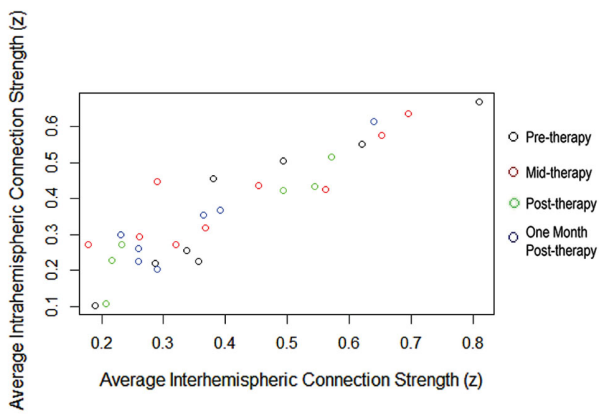

FIGURE 3 | Average within-subject interhemispheric and intrahemispheric connection strengths correlated throughout the BCI therapy study period.

contralesional thalami in this study, in particular the precuneus, cerebellum, cingulate, and anterior cingulate, have been implicated in a number of cognitive processes including visuospatial imagery (Cavanna and Trimble, 2006; Timmann and Daum, 2007), motor coordination and learning (Fine et al., 2002), attention (Timmann and Daum, 2007), learning (Bussey et al., 1996), memory (Kozlovskiy et al., 2012), and reward-based learning (Shenhav et al., 2013). These results suggest that a learning process may constitute a critical component of therapy using this BCI device.

Subject performance on the BCI task, which was maintained a relatively constant accuracy over sessions while task difficulty gradually increased with time (**Figure 1**), also supports the hypothesis that therapy using this BCI system promotes an adaptive learning process. In this experiment, subjects effectively learned to achieve greater and greater degrees of neuromodulatory control in order to regain a target level of accuracy when faced with increasingly difficult tasks. In contrast to the phenomena of learned non-use sometimes observed in stroke survivors (Taub, 1976), BCI therapy allows for the practice of modulating behavioral, muscular, and neuronal output for goal attainment in a novel learning environment with multi-modal feedback. If viewed as an operant conditioning mechanism, BCI therapy may thereby facilitate neuroplasticity through this reinforcement of central-peripheral connections (Hebb, 2005).

That the connections found to correlate in degree of change with changes in behavioral outcomes were also largely thalamic connections further underscores the importance of

Table 3 | Correlations between changes in motor network connectivity with changes in behavioral outcome measures.

Measure	Pearson's *r*	Correlation *p*-value	GEE *p*-value
ARAT	−0.458	0.049*	0.345
9-HPT	−0.640	0.010*	3.303×10^{-6}*
SIS ADL	0.635	1.023×10^{-4}*	1.796×10^{-4}*
SIS HF	0.518	0.011*	0.038*

**Significant at $p < 0.05$. ARAT = Action Research Arm Test, 9-HPT = Nine-Hole Peg Test, SIS ADL = Stroke Impact Scale—Activities of Daily Living, SIS HF = Stroke Impact Scale—Hand Function.*

understanding the role of thalamic FC in the process of motor recovery after stroke. An examination of the relationships between these individual connections—thalamic and non-thalamic—and the behavioral measures studied also shows that both adaptive and maladaptive changes may have been present. Namely, while performance on most behavioral measures studied tended to improve with improved FC strength, ARAT performance was negatively correlated with increased connectivity between the ipsilesional thalamus and ipsilesional cerebellum and between the contralesional primary motor cortex and the contralesional supplemental motor area. The simultaneous development of adaptive and maladaptive changes in functional connection strengths during the process of stroke recovery has been documented in a previous study (Wang et al., 2010) similar to the findings presented here, while others have identified changes in FC that may facilitate motor recovery (Rosso et al., 2013). The role of such changes in the process of stroke recovery and the way in which such changes may be modulated through the use of traditional and experimental rehabilitative therapies remains to be fully characterized and understood. However, the presence of both adaptive and maladaptive connections may represent a period in an ongoing recovery process in which both types of connections are formed and subsequently modified, similar to that of synaptic pruning and strengthening observed during the learning and aging processes of normal development (Hebb, 2005).

Another factor that may have contributed to the development of maladaptive functional connections is the possibility that insufficient or unreliable feedback from the BCI device, which might be evidenced by poor BCI task performance, could result in frustrating the participant with the unintentional reinforcement of maladaptive neural activity patterns. While the subjects in this study were able to perform significantly better than chance when using the BCI device, performance accuracy was not necessarily at or above 70%—a common threshold used to indicate adequate BCI control. However, the use of 70% as a threshold for BCI performance appears to stem from earlier studies in which this level of accuracy was needed for communication using a Language Support Program (Kubler et al., 2001, 2005). There appears to be less evidence supporting the use of 70% as a threshold for performance accuracy when no communicative purpose is intended for the BCI system, and in fact significant variation in individual ability to control similar BCI cursor tasks can persist even after 10 sessions of training (McFarland et al., 2005).

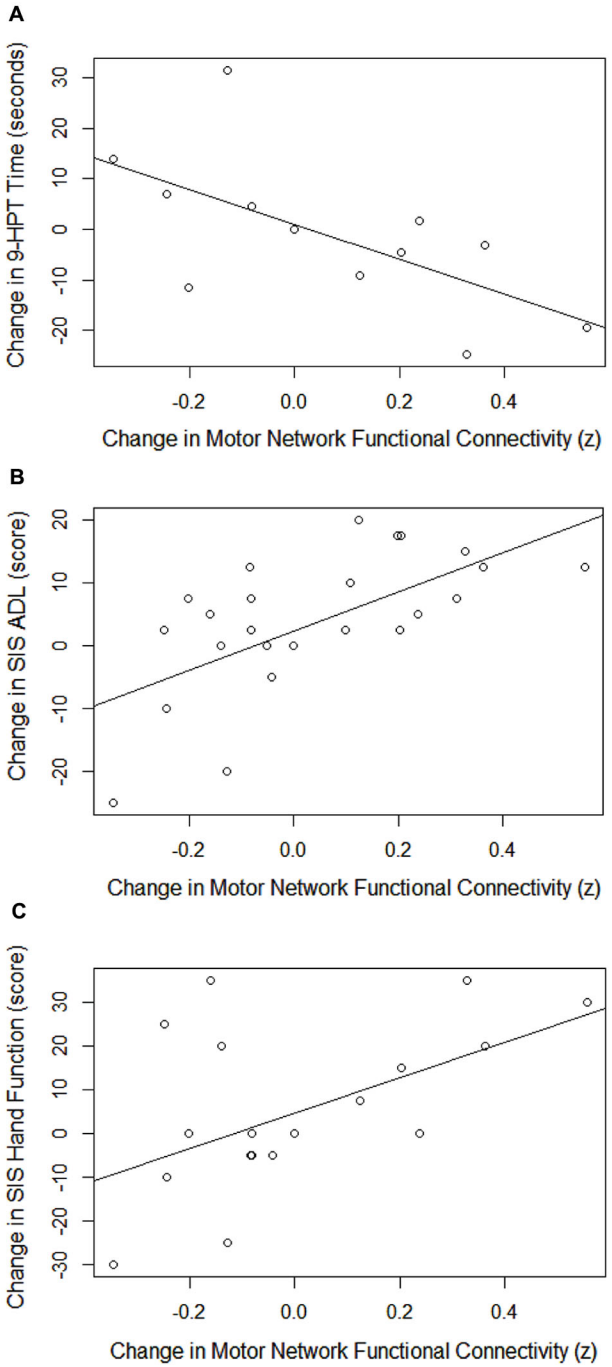

FIGURE 4 | Correlations between changes in motor network FC with changes in 9-HPT performance (A), SIS ADL scores (B), and SIS HF scores (C). 9-HPT = Nine-Hole Peg Test, SIS ADL = Stroke Impact Scale—Activities of Daily Living, SIS HF = Stroke Impact Scale—Hand Function.

It is also known that at least some of the literature exploring human performance in BCI tasks demonstrating consistent performance greater than 70% tends to be biased in favor of good performers. This bias stems from the fact that poor performers are seldom invited to return for further testing (Fazli et al., 2009), do

Table 4 | Correlations between changes in connection strength of individual motor network functional connections and changes in behavioral outcome measures.

Behavioral Measure	Seed-seed Covariation	Pearson's *r*	Correlation fdr-corrected *p*-value	GEE analysis *p*-value
9-HPT	I thalamus—C primary motor cortex	−0.669	0.023	0.009
	I thalamus—I primary motor cortex	−0.678	0.023	8.123×10^{-75}
	C thalamus—C primary motor cortex	−0.851	6.36×10^{-4}	1.110×10^{-6}
ARAT	I thalamus—I cerebellum	−0.677	0.011	0.027
	C primary motor cortex—C supplementary motor area	−0.677	0.011	7.213×10^{-5}
SIS HF	I thalamus—C cerebellum	0.790	8.028×10^{-5}	0.006
	I cerebellum—C cerebellum	0.547	0.025	0.016
	I thalamus—I primary motor cortex	0.632	0.007	0.003
SIS ADL	C thalamus—C primary motor cortex	0.686	2.315×10^{-4}	0.001

I = ipsilesional, C = contralesional, ARAT = Action Research Arm Test, 9-HPT = Nine-Hole Peg Test, SIS ADL = Stroke Impact Scale—Activities of Daily Living, SIS HF = Stroke Impact Scale—Hand Function.

not always have their performance accuracy reported (McFarland et al., 2008), and are not always allowed to continue the full course of BCI training, thereby excluding them from final accuracy reports (Wolpaw et al., 1991). In studies with no indication that good performers have been preferentially enrolled, accuracies over approximately 20 or more training sessions on BCI cursor tasks can range from just above 20% to >90% depending on game play parameters and individual performance (Wolpaw and Mcfarland, 1994, 2004; McFarland and Wolpaw, 2003). Furthermore, game play parameters were dynamically adjusted in this study to make the game more difficult as subjects achieved 70% accuracy at a given level or difficulty. Therefore, subject performance in this study is not necessarily expected to be at or above 70% when averaged over all trials because subjects were not given the opportunity to perform with greater than 70–80% accuracy for long stretches of training without game difficulty increasing.

While subject performance accuracy is readily calculable based on the numbers of successful and unsuccessful trials, it is more difficult to assess the accuracy of the feedback presented based on task performance. This is because a subject may fail to achieve greater than 70% accuracy even with a perfectly calibrated BCI feedback system if the individual's ability to modulate their Mu/Beta desynchronization is not well controlled. Still, it may be that imperfect feedback effectively lowered the performance accuracy of the subjects studied, thereby frustrating the subjects and affecting subject motivation and engagement with the therapy task. Imperfect feedback may also have contributed to the formation of the maladaptive changes in FC observed, potentially rewarding suboptimal patterns of neural activity during movement attempts or discouraging patterns that would have been truly optimal. Nevertheless, it is worth noting that even imperfect feedback during BCI therapy would constitute a more reliable form of neurofeedback than the absence of such feedback that is available during standard of care therapies such as traditional physical and occupational therapy.

It will be key in future studies to determine whether the rehabilitative effects of BCI therapy can be adequately achieved with the attempted use of an imperfect feedback system or if both feedback accuracy and subject performance accuracy should be further optimized before additional feedback modalities and increased task difficulty are applied. In conducting the experiment described in this paper, many subjects actually expressed a desire for the task to be made more difficult so that the game was not "too easy" or "boring", even in cases where the participants were not consistently achieving 80–100% accuracy. Changes in game parameters to increase task difficulty appeared to help keep subjects engaged with the BCI therapy. To this end, future studies may also serve to better characterize the tradeoff between increased thresholds for feedback and performance accuracy and the benefits of maintaining subject engagement and motivation throughout the therapy period.

There has been much interest in understanding the relative contributions of interhemispheric and intrahemispheric FC to motor recovery after stroke. Studies of acute stroke patients have shown decreases in interhemispheric connectivity in the motor cortex compared to healthy controls (Carter et al., 2010; Golestani et al., 2013; Xu et al., 2014). Such disruptions have been shown to correlate with ARAT performance in the acute stage of stroke only when interhemispheric connections are considered (Carter et al., 2010). Similarly, increases in interhemispheric but not intrahemispheric FC between homologous regions of the primary sensorimotor cortex have been shown to correlate with Motricity Index scores during the first year of recovery (Xu et al., 2014), and some patients with full recovery 90 days after stroke show a return to normal motor connectivity within the same time frame (Golestani et al., 2013). Homotopic interhemispheric connectivity of the motor cortex has also been shown to correlate with motor function in chronic stroke patients (Chen and Schlaug, 2013; Urbin et al., 2014). Our analysis found no such differentiation between interhemispheric and intrahemispheric functional connections, suggesting that the

BCI therapy administered contributed to brain-behavior changes mediated by a whole-network effect, with both individual intrahemispheric and interhemispheric connections showing significant relationships with behavioral gains. Nevertheless, it may be worth noting that both individual functional connections found to be negatively correlated with changes in ARAT performance were intrahemispheric. Few studies have explored changes in FC with BCI therapy. In one study, increases in FC between the bilateral supplemental motor area and areas beyond the motor network correlated positively with gains in Fugl-Meyer scores after BCI therapy (Varkuti et al., 2013). Future studies of FC changes after stroke with spontaneous and facilitated recovery will enhance the understanding of how these changes relate to motor gains and how such relationships may differ based on patient and therapy characteristics.

At the network level, it has been suggested that motor recovery following stroke may be enhanced with reactivation of the motor network along with therapy that allows for adaptive motor network reorganization (Calautti and Baron, 2003). The strong correlation between the average strengths of inter- and intrahemispheric connections throughout the therapy period also supports the idea that the changes in FC seen with BCI therapy in this group of subjects were effected at the whole-network level rather than through the selective strengthening or weakening of one class of connections. Increases in connectivity within the motor network also correlated to changes in 9-HPT performance as well as changes in SIS ADL and SIS HF scores. It is important to note that this relationship with 9-HPT performance can only be said to exist among the higher-functioning subjects included in the study, as those with more significant impairments were unable to complete the assessment and therefore omitted from the analysis. While different patterns of FC change have been documented in severely impaired stroke patients relative to their mildly impaired counterparts (Rosso et al., 2013), the persistence of significant relationships between motor network connectivity and 9-HPT performance as well as with the subjective SIS domain scores, which included subjects at all levels of impairment, suggests the presence of a similar effect in the more impaired subjects as well. Furthermore, the difference in behavioral measure changes during the pre-therapy period relative to those observed during the BCI therapy period hints that the BCI therapy administered may be implicated in the effect.

Unfortunately it is not possible at this time to make statistical comparisons with the limited amount of data from subjects who underwent additional assessments during a pre-therapy period, which would allow for a clearer understanding of the effect of the BCI therapy administered. It is similarly difficult to disambiguate the relative contributions of the various components of therapy using this BCI system to the effects observed. This study remains limited in that it cannot establish the degree to which the changes observed are attributable to the neurofeedback aspect of the BCI therapy and how much of these same phenomena may be due to other aspects of therapy with this system, such as repetitive practice or functional electrical stimulation. Nevertheless, BCI performance results suggest that participant engagement with the neurofeedback task persisted throughout the therapy period, and both BCI performance and neuroimaging findings support the existence of an active learning process over the course of therapy as previously discussed. Therefore, it would seem that the neurofeedback component of BCI therapy is likely to contribute to the effects described in this study, as it demands consistent engagement from each participant and is the only component of the BCI system described that allows for reward-based neuromodulatory training.

Other limitations of this work include the use of a relatively small sample of heterogeneous subjects, which may have resulted in some analyses being insufficiently powered to detect smaller changes or more subtle relationships, especially after floor and ceiling effects were accounted for in analyses that incorporated behavioral data. The brain-behavior relationships observed also remain correlational, with potential causal mechanisms underlying these relationships only speculative based on the data available. To help address some of these issues, future work will aim to study larger cohorts with a more robust seeding of the motor network in order to allow for a more thorough representation of motor network regions and a better description of the FC changes that occur. Future studies will also benefit from the incorporation of data from a larger pre-therapy or control group in order to differentiate the effects of the BCI therapy from other factors such as practice effects, as well as from designs in which groups receiving passive repetitive stimuli can be compared to groups receiving stimuli triggered by neurofeedback in order to better isolate the effect of the neurofeedback component of these types of devices. As the understanding of the mechanisms by which BCI therapies may induce changes in both FC and behavioral motor function improves, these insights may be used to guide the development of future devices better targeted to the needs of the patients who use them.

AUTHOR CONTRIBUTIONS

Brittany M. Young assisted in subject recruitment, data collection, data analysis, and writing. Zack Nigogosyan assisted with data collection and writing. Alexander Remsik assisted with data collection and writing. Léo M. Walton assisted with data collection and writing. Jie Song assisted with subject recruitment and data collection. Veena A. Nair assisted with subject recruitment, data collection, data analysis, and writing. Scott W. Grogan assisted in data collection. Mitchell E. Tyler provided TDU hardware and expertise. Dorothy F. Edwards assisted with study design and data analysis. Kristin Caldera assisted with subject recruitment. Justin A. Sattin assisted with study design and subject recruitment. Justin C. Williams is one of two lead PI's on this project and supervised the technical and engineering aspects of the work. Vivek Prabhakaran is one of two lead PI's on this project and supervised the neuroimaging and neuroscience aspects of this work.

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Movement-related cortical potentials in paraplegic patients: abnormal patterns and considerations for BCI-rehabilitation

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Non-invasive EEG-based Brain-Computer Interfaces (BCI) can be promising for the motor neuro-rehabilitation of paraplegic patients. However, this shall require detailed knowledge of the abnormalities in the EEG signatures of paraplegic patients. The association of abnormalities in different subgroups of patients and their relation to the sensorimotor integration are relevant for the design, implementation and use of BCI systems in patient populations. This study explores the patterns of abnormalities of movement related cortical potentials (MRCP) during motor imagery tasks of feet and right hand in patients with paraplegia (including the subgroups with/without central neuropathic pain (CNP) and complete/incomplete injury patients) and the level of distinctiveness of abnormalities in these groups using pattern classification. The most notable observed abnormalities were the amplified execution negativity and its slower rebound in the patient group. The potential underlying mechanisms behind these changes and other minor dissimilarities in patients' subgroups, as well as the relevance to BCI applications, are discussed. The findings are of interest from a neurological perspective as well as for BCI-assisted neuro-rehabilitation and therapy.

Keywords: EEG, movement related cortical potentials, spinal cord injury, central neuropathic pain, BCI

INTRODUCTION

Movement-related cortical potentials (MRCP) reflect brain electrical activity related to the execution of overt or covert movements. MRCP resulting from either imagery or attempt of motor volition are often investigated in a cue-based paradigm (MacKay and Bonnet, 1990; Ulrich et al., 1998). In paired cue-based paradigms for Brain-Computer Interfaces (BCI), the user is asked to prepare for a movement following the first cue and to execute the movement following the second cue. The readiness potential, which is the leading part of the MRCP and precedes the movement execution, may be movement specific (Shibasaki et al., 1980) when there is only one movement option, or may present general preparation for an action (Walter et al., 1964) when there are several choices for movements. Following the execution cue, the MRCP comprises components known as premotor positivity (Deecke et al., 1976; Castro et al., 2013), motor potential (Deecke et al., 1969) and reafferent potential (Bötzel et al., 1997) related to the kinesthetic feedback once the movement has occurred.

MRCPs are influenced by impairments of the sensory-motor system. Castro et al. (2013) compared MRCPs in three subject groups: healthy individuals who executed movement of the left and right leg, healthy subjects who only prepared for the same movements, and chronic complete spinal cord injured (SCI) patients who imagined the same movements. They observed that the amplitudes of the readiness potential and motor potential were lower in SCI patients than in healthy subject executing the movement, but were comparable between SCI patients and healthy participants who only prepared for the movements. All SCI patients had a complete injury with no preserved sensation under the level of the injury, thus in that study it was not possible to distinguish the effects of sensory and motor loss, specifically complete/incomplete injury in the sensory pathways. Therefore, our first research question is related to the role of sensory information, which can be investigated in complete/incomplete SCI subgroups.

A frequently overlooked co-morbidity of paralysis is Central Neuropathic Pain (CNP), present in 40% of the SCI population, equally affecting paraplegic and tetraplegic patients with complete or incomplete injury (Siddall et al., 2003). CNP is a consequence of an injury to the somato-sensory system (Haanpää et al., 2011),

and as such it originates at the cortical level. Functional magnetic resonance imaging (fMRI) studies showed that this type of pain modulates the activity of the motor cortex (Gustin et al., 2010) of both paralyzed "painful" limbs and non-paralyzed limbs. In a recent study, Vuckovic et al. (2014) compared event-related synchronization/desynchronization (ERD/ERS; Pfurtscheller and Lopes Da Silva, 1999) in patients with paraplegia and CNP, patients with paraplegia and no pain and healthy individuals with no pain. Patients with CNP had strongest ERD in the theta, alpha and beta bands, while ERD was less expressed in healthy participants. Patients with no pain (PNP) had the weakest ERD. However, it is not clear if the presence of CNP would equally affect MRCP and ERD/ERS, as it is believed that the two signal modalities have different origins (Babiloni et al., 1999; Pfurtscheller and Lopes Da Silva, 1999). This raises our second research question: the role of pain in MRCPs of SCI patients, which can be studied in pain/no-pain SCI subgroups.

The role of abnormality patterns in MRCP is relevant in BCI-rehabilitation applications. Recently a BCI system based on MRCP was proposed and tested on healthy subjects and stroke patients (Niazi et al., 2011, 2013; Xu et al., 2014a,b). The MRCP was used in this system as a trigger signal (brain switch) to control an external device, such as function electrical stimulation (FES) or an active orthosis. This paradigm was shown to promote activity-dependent cortical plasticity in healthy subjects (Mrachacz-Kersting et al., 2012; Niazi et al., 2012; Xu et al., 2014b) and stroke patients (Mrachacz-Kersting et al., 2013). SCI patients with incomplete injury are ideal candidates for a combined sensory-motor therapy, as the one proposed by using the MRCP as brain switch. However, the characteristics of MRCPs in these patients are not known yet and this information is relevant for the design of a detector based on MRCP waveforms. Hence, the implication on potential applications of BCI for SCI patients is the third research question we will address.

This study presents the initial step in developing an MRCP-based BCI system for SCI patients. For this purpose, we investigated the difference in MRCP morphology between SCI patients and healthy subjects, as well as the unique features of MRCP in sub-groups of patients with different degrees of CNP and scale of impairment (complete or incomplete paralysis). Further, the related issues for BCI rehabilitation are discussed.

METHODS

SUBJECTS

Eight healthy volunteers (HV) and 14 SCI patients, with either complete or incomplete paralysis, participated in this study. The neurological level of injury was determined using the American Spinal Injury Association (ASIA) Impairment Classification (Marino et al., 2003). SCI patients were further classified on the basis of presence or absence of CNP, below the level of the injury. Inclusion criteria for patients with pain (PWP) was that they were at least 1 year post-injury, were treated for CNP for at least 6 months, had a pain level $\geq$5 on the Visual Numerical Scale (VNS) and had the injury at level T1 or lower. Inclusion criteria for PNP were that they were at least 1 year post-injury, with injury at level T1 or lower. General exclusion criteria for all three groups were age under 18 or over 55, existence of any other chronic or acute pain at the time of the experiment, brain injury or other known brain condition that would influence EEG interpretation or would prevent the patients from understanding the experimental task. Details about the subjects' self-reported information are presented in **Table 1**.

Informed consent was obtained from all participants, and the study protocol was approved by the University of Strathclyde Ethical Committee for the HV group and the National Health Service for Greater Glasgow and Clyde Ethical Committee for the SCI group.

EXPERIMENT PROTOCOL

The participants were comfortably seated at a desk, at a distance of approximately 1.5 m from the computer screen on which visual instructions were provided. They were instructed to look at the center of the screen and to perform motor imagery following visual cues while minimizing eye movements. For each trial, at $t = -1$ s a readiness cue (a cross +) appeared and would remain for 4 s (**Figure 1**). At $t = 0$ s an initiation cue, presented as an arrow, appeared next to the cross sign, for a duration of 1.25 s. The arrow pointed either to the left, right or down, corresponding to the motor imagery tasks of left hand waving (LH), right hand waving (RH) and tapping with both feet (F), respectively. The participants were asked to continue to perform imaginary movements until the cross disappeared from the screen (3 s after the initiation cue appeared). In total, 60 trials of each of the three type of motor imagery were performed by each subject in one session. The trials were divided in groups of 10 for each type of imaginary movement (LH, RH and F). Sequences of motor imagery tasks appeared in a random order and at random 3–5 s intervals.

We instructed the participants to perform motor imagery, and we asked them specifically to imagine, not to attempt movements. However, it should be noted that while HV practiced motor

Table 1 | Patient information.

Nr	Level of injury	ASIA*	Time after injury	Pain VNS‡	Years with pain
1	T5	A	7	7	7
2	L1	B	15	7	15
3	T6/T7	D	4	7	3
4	T6/7	B	25	10	24
5	T6	B	N/A	N/A	N/A
6	T8	B	11	9	11
7	T12	B	33	6	4
8	T7	A	7	/	/
9	T7	B	7	/	/
10	L1	A	6	/	/
11	T2	A	2	/	/
12	T5	B	15	/	/
13	T4	A	9	/	/
14	T7	A	15	/	/

* *ASIA stands for the American Spinal Injury Association, whose impairment classification was used to determine the neurological level of injury.*

‡ *VNS is Visual Numerical Scale, which was used for pain level assessment.*

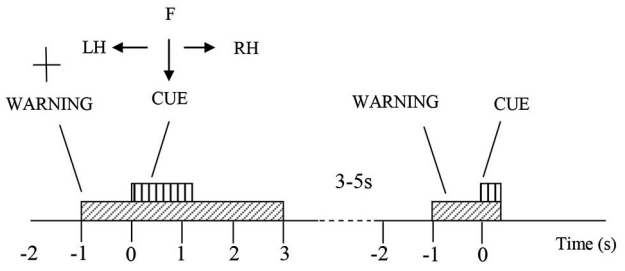

FIGURE 1 | Experiment protocol. At $t = -1$ a cross appears on the screen, indicating the participant should prepare for a motor imagery. One second later, an arrow pointing to right, left or down, and the participant were asked to perform a motor imagery of their right hand (RH), left hand (LH) or feet (F) accordingly, till the cross disappear at $t = 3$ s. Afterwards there is a rest period of 3–5 s, before the next trial begins.

imagery, SCI patients might have also attempted to move their paralyzed limb.

A 61-channel EEG recording was performed with an EEG device (Synamps^2, Neuroscan, USA). The electrodes were placed according to the standard 10-10 locations. EOG was recorded from three channels around the right eye. EEG and EOG were recorded with respect to the linked ear reference and the ground was at AFz. In addition, EMGs were recorded from the right and the left wrist extensor muscles and right foot dorsiflexor using the bipolar inputs to the Synamps device. The purpose of EMG recording was to check for the absence of any voluntary movements when the subjects attempted motor imagery. The sampling frequency was 1000 Hz. The electrode impedance was kept below 5 kΩ during all measurements.

SIGNAL PRE-PROCESSING

The EEG signal was down-sampled to 250 Hz and pre-processed with a band-pass filter at 0.1–3 Hz (second order butter-worth), followed by the large Laplacian filter of the respective central channels (Cz and C3 for foot and right hand, respectively) and eight second-nearest channels around them (Fz, FC1, FC2, C3, C4, CP1, CP2, and Pz for foot, and F3, FC5, FC1, T7, Cz, CP5, CP1, and P3 for right hand, respectively). This was done to reject the common mode noise and thus increase the signal-to-noise ratio (McFarland et al., 1997; Niazi et al., 2011). For each trial, the segments between $t = -2$ s and $t = 6$ s, with respect to the cue onset, were extracted as MRCP. All trials were visually inspected to reject trials that were potentially corrupted by artifacts and noise. All trials were of good quality and no trial needs to be rejected.

STATISTICAL ANALYSIS OF MRCP MORPHOLOGY ACROSS SUBJECT GROUPS

We performed the following three pair-wise analyses:

1. **HV vs. SCI**: healthy volunteers vs. all SCI patients independent of the level of injury or the presence of pain (8 HV vs. 14 SCI);
2. **PNP vs. PWP**: SCI patients with no pain vs. SCI patients with CNP (7 PNP vs. 7 PWP). Both PNP and PWP group contained patients with complete and incomplete injury;
3. **CP vs. IP**: SCI patients with complete injury (ASIA A complete loss of motor and sensory functions under the level of the injury) vs. SCI patients with incomplete injury (ASIA B/C/D with some sensations preserved under the level of the injury) (6 CP vs. 8 IP). Both CP and IP groups contained patients with and without pain.

In order to compare MRCP morphology between groups, a Wilcoxon rank-sum test was utilized for statistical analysis. Three comparisons were performed for each type of movement imagery. The null hypothesis was that, for each type of movement within each group, the MRCPs have the same average value at the same temporal location. For each comparison, the entire 8 s long interval was divided into 0.1 s long segments and statistical analysis was performed between groups separately for the 80 segments of each case. The statistical significance level was set to 0.05, with a Holm-Boniferroni correction (Holm, 1979) applied (smallest p-value was 0.05/80).

CLASSIFICATION OF MRCPs

Following the above statistical analysis, a two-class classification was performed on MRCPs of each task (feet and right hand) corresponding to the three pairs defined above, i.e., HV vs. SCI, PNP vs. PWP, and CP vs. IP. The classification was performed with a dimensionality reduction algorithm called locality persevering projection (LPP; He and Niyogi, 2003; He et al., 2005), followed by a k-nearest-neighborhood (kNN) classifier. LPP, a manifold-based method, was demonstrated to be superior than linear methods such as PCA and LDA when data have clear nonlinear characteristics (He et al., 2005). LPP can preserve the data structure in the original manifold when projecting data into lower linear feature space, of which classic linear dimensional reduction algorithm such as PCA or SVD is not capable. It was previously used for MRCP detection, in which it outperformed linear match filter method (Xu et al., 2014a). A five-fold cross-validation was used to validate the classification accuracy. The classifier was trained with randomly selected 4/5 of single-trial MRCPs and the remaining 1/5 were considered as testing sets. The LPP algorithm was used to project the training samples into a lower dimensional space, while preserving its intrinsic structure in its original manifold, as in Xu et al. (2014a). The reduced dimension was chosen as 60% of the original data dimension, which was proved to be optimal for MRCP detection (Xu et al., 2014a). Next, the projected data in this LPP subspace were used to train the classifier. In the subsequent testing step, testing samples were projected into the LPP sub-space obtained through training, which was then classified using the trained kNN into either class of the pair (e.g., HV or SCI). The classification performance was quantified with the classification accuracy, i.e., the percentage of correctly classified trials with respect to the total number of testing trials.

Aiming at investigating the temporal discriminant information in the MRCPs among different groups, the classification was not performed on the entire MRCP segments, but with processing window of segments at different temporal location as well as with different segment lengths. This process was done by sliding the starting point of the processing window, from $t = -2$ s

to t = 3 s (step size 0.1 s). At each starting point, the length of the window also changed from 1 s to 3 s (step size 0.1 s). As the movement imagery was performed until t = 3 s, it was not practically useful to process signals 3 s after the movement onset.

RESULTS

MRCP MORPHOLOGY

The MRCPs of foot imagery are compared for the subject groups (i.e., HV vs. SCI, PNP vs. PWP, and CP vs. IP) in **Figure 2**. The amount of MRCP segments is equal to the product of number of trials and number of subjects. As stated in Section Experiment Protocol, the number of trials is 60 for each type of task by each subject. E.g., we had 8 HV and 14 SCI, the amount of segments for HV and SCI is 480 and 840, respectively. The difference is particularly pronounced for the case of HV vs. SCI. In general, the amplitude of MRCP for the SCI group was significantly greater than that for the HV group (peak-to-peak value: 5.6 ± 6.3 μV vs. 2.7 ± 3.4 μV). The CP group's MRCP amplitude was also slightly greater than the IP group, while there was only a small difference in amplitude for PNP vs. PWP. The evoked responses following the readiness cue (the "+" sign) and the initiation cue (arrows) are clearly visible in all cases.

Period of general preparation for movement

During the period t = −1 s to t = 0 s, i.e., after the "+" appeared and before the arrow appeared, SCI subjects had a significantly larger positivity than HV subjects. This significant difference lasted until −0.7 s, i.e., 300 ms after the appearance of the "+" sign. This is an indication of altered (enhanced) response to a movement related visual cue from the SCI patients. A significant difference was found for the CP vs. IP group: CP patients had larger visual-motor positivity than IP subjects. This result suggested that complete loss of sensory information (CP group) from the foot enhanced the potential, compare to subjects with some remaining sensory input (IP group). These results imply that the level of deafferentation is positively related to the magnitude of visual evoked potentials. On the other hand, no statistical significance was found in the PWP vs. PNP group, indicating that presence of pain does not affect the magnitude of the preparation potentials.

The visual-motor potential from motor imagery of the hand at C3 during this period (**Figure 3**) was smaller in magnitude compared with that of foot imagery at Cz. For HV vs. SCI groups, similar to foot imagery, a difference was found around −0.7 s. The difference did not reach statistical significance, probably because it was much smaller both in amplitude and duration than in the case of foot imagery. No statistically significant difference was observed for the CP vs. IP group. Similar to the case of foot imagery, no significant difference was found for PNP vs. PWP group.

A difference at Cz between HV and PWP is because SCI had stronger positivity at around t = −0.7 at Cz (painful limbs) than they had at C3 which corresponds to a non-paralyzed limb. It is true that we showed Cz for MI of legs and C3 for MI of right hand, but we also checked that SCI has larger positivity at Cz than HV

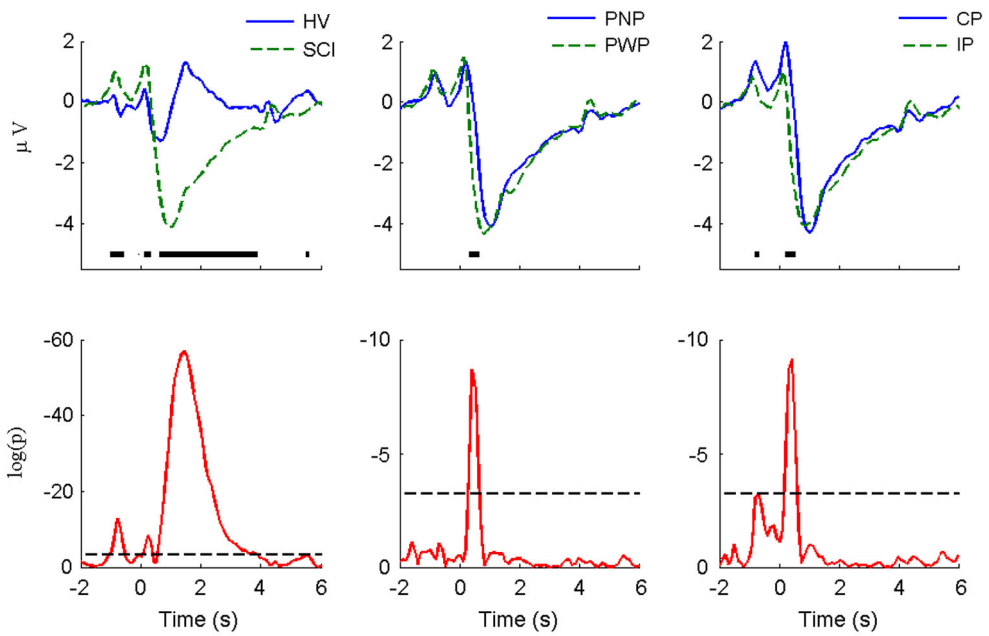

FIGURE 2 | MRCP morphology and statistical comparison for large Laplacian Cz (motor imagery of foot). The figures in the upper row present the average MRCP from different groups (HV vs. SCI, PNP vs. PP, and CP vs. IP). The thick horizontal lines indicate the portions in which statistically significant difference was detected using the Wilcoxon rank-sum test with Holm-Boniferroni correction. The *p*-values of the statistical tests were presented in the lower row, with logarithm scale (log*p*). The dashed horizontal line indicates the minimal significance level in the Holm-Bnifeernoi correction procedure, i.e., log(0.05/80), since there were 80 simultaneous tests in each case.

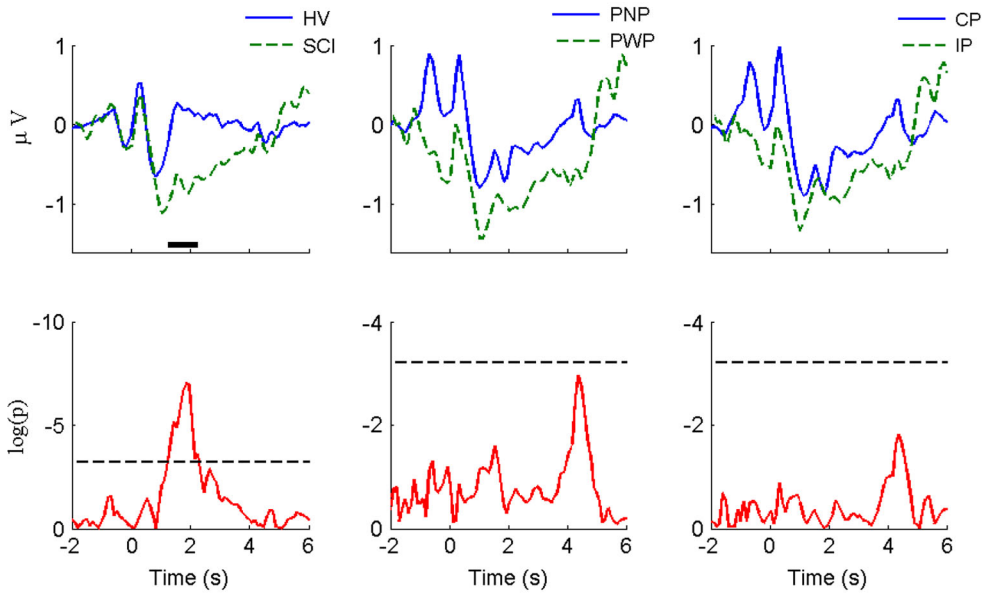

FIGURE 3 | MRCP morphology and statistical comparison for large Laplacian C_3 (motor imagery of right hand). The convention and legends are the same as in **Figure 2**.

even for motor imagery of hands. For HV there does not seem to be a difference between Cz and C3 in a period $t = -1$ s to $t = 0$ s.

In summary, during this period of general preparation for movement, the subjects did not know what type of motor imagery should be performed, so the visual-motor potential was not task-specific. Therefore, the consistent results between foot imagery and hand imagery, other than the overall magnitude difference, are expected. This is particularly the case for HV vs. SCI group, where significance was detected at this point for foot imagery. While for hand imagery a distinct peak of the *p*-value existed, no statistical significance could be established.

Period of movement specific-preparation and covert motor execution

As presented in **Figure 2**, during the period of $t = 0$ s to $t = 3$ s of foot motor imagery, a statistically significant difference can be noticed in all three pairs of comparisons. The largest difference was observed between HV and SCI. SCI patients had significantly larger amplitude of the positive peak at 300 ms. The MRCP negativity of the SCI group was also significantly larger than for the HV subjects. The rebound from the negativity of the HV group appeared around $t = 1$ s and then returned back to baseline around $t = 3$ s; for the SCI group, the rebound was more gradual, reaching the baseline at approximately $t = 6$ s without a second positive peak. The main difference between PNP group and PWP group was located between $t = 0$ s and $t = 1$ s, where descending for the PWP group was faster than that for the PNP group. Similarly the largest difference between CP and IP group could be noticed in the first 0.5 s following the directional cue. The CP group presented higher amplitude of the positive peak and faster decreasing slope than IP group.

For hand imagery, the differences after the initialization cue were much smaller than difference for feet imagery for all groups. This is expected since none of the subjects had sensory or motor impairments of the upper extremities. Still, there was a statistically significant difference between HV and SCI groups in part of the rebound phase (from 1.2 s to 2.3 s). However, there is no statistical difference between PNP and PWP group and between CP and IP group.

In summary, largest differences during the period following the directional cue were noticed, as expected, between HV and SCI group and they were present for both paralyzed and non-paralyzed limbs. Smaller differences, both in magnitude and duration, also existed between PWP and PNP group and for CP and IP group, for motor imagery of feet. However no statistically significant difference was observed for motor imagery of right hand in either of the patient sub-groups.

CLASSIFICATION PERFORMANCE

Figure 4 illustrates the classification accuracies of the three groups, as a function of the starting point and the length of the processing windows. It was possible to classify between foot imagery of the HV and SCI group with higher accuracy than the two patient sub-groups (**Figure 4**). This is in accordance with the largest statistical difference found between the MRCP of HV vs. SCI, as presented in **Figure 2**.

The highest average accuracy of HV vs. SCI was 90.5% (at window start = −1 s and window length = 3 s), while those of PNP vs. PWP and CP vs. IP were 68.7% (at window start = −0.1 s and window length = 1.4 s) and 65.1% (at window start = 0.2 s and window length = 2 s), respectively.

In addition, the accuracies changed according to the window start and length, and the patterns of this change are different

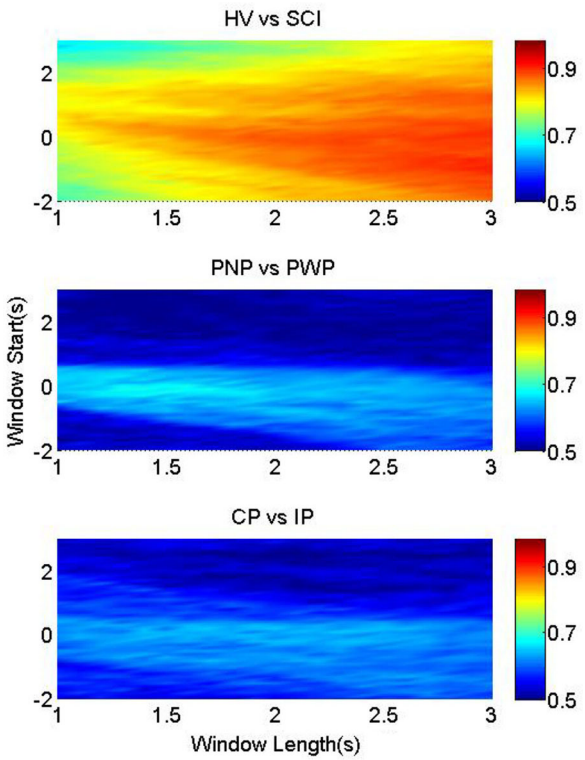

FIGURE 4 | Classification accuracy for foot imagery. The color-bars identify the classification accuracies of MRCP segments from three pairwise groups, with onset from $t = -2$ s to $t = 3$ s, and length between 1 s and 3 s. These three figures from upper to bottom represent the results of HV vs. SCI, PNP vs. PWP, and CP vs. IP, respectively.

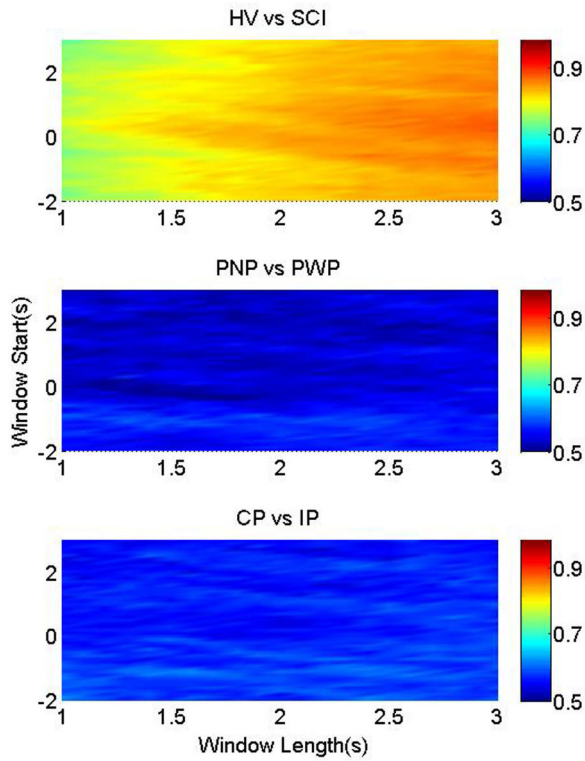

FIGURE 5 | Classification accuracy for right hand. The color-bars identify the classification accuracies of MRCP segments from three pairwise groups, with onset from $t = -2$ s to $t = 3$ s, and length between 1 s and 3 s. These three figures from upper to bottom represent the results of HV vs. SCI, PNP vs. PWP, and CP vs. IP, respectively.

among the three pairwise groups. For HV vs. SCI, the part with accuracies ∼90% was located in the bottom right corner, where the starting point was mostly before $t = 0$ s, and the length was larger than 2.5 s. High classification accuracies (74%) were achieved even when only a 1 s period of general preparation ($t = -1$ s till $t = 0$ s) was used to classify between the two groups. As the analysis time window moved towards the movement specific period, shorter windows were sufficient to achieve high classification accuracy, indicating largest difference between HV and SCI during the period of task specific motor imagery. This high classification performance resulted from the large difference in MRCPs between HV and SCI, as shown in **Figure 4**.

Similar observation holds for motor imagery of the right hand (**Figure 5**), indicating a general influence of paralysis on the signal characteristics. This indicates that paralysis globally changes preparation of movement, not restricted to the paralyzed limb.

Nevertheless, the distributions of accuracies for the other two groups are notably different. For imaginary movement of feet the higher accuracy (>65%) part for PNP vs. PWP were limited in a small strip around window onset $t = 0$ s, with window length of 1.2–1.7 s. This strip with higher classification accuracy exactly matched the MRCP range with lower p-values, and higher statistical significance in **Figure 2**. These results indicate statistically significant difference between these two groups in a period of general preparation and in the period of the early preparation/initiation of the covert movement.

The area with accuracies higher than 60% for CP vs. IP was also small, but the shape was evidently different from that of PNP vs. PWP. It was an approximately horizontal strip where the onset was around $t = 0$ s and the length ranges from 1.5 s to 2.5 s. This shows that preserved sensation do not considerably influence MRCP in the general preparation of movement but it does influence preparation for specific movement of a part of the body with preserved sensation vs. part of the body with no sensation.

The classification rate between PNP and PWP in motor imagery of the right hand could reach 50% only if the period of general preparation was included in the analysis. This indicates that the presence of CNP influences the general preparation of movement in the painful/non-painful and paralyzed/non-paralyzed limb. In a study on the ERS/ERD of the same group of patients (Vuckovic et al., 2014), a generalized influence of pain on movement of painful and non-painful limbs was also found.

For right hand between CP and IP group, classification accuracy was slightly higher for the period of general preparation, but it has no clear pattern anywhere else.

DISCUSSION

This study presented analysis of the difference in MRCP morphology of covert movement between HV and patients with spinal cord injury, through direct statistical comparison and through pattern classification. This has implications on performance of BCI control systems based on MRCP which has mostly been tested on healthy individuals.

The aim of this study was to compare MRCP between HV and patients during both general and movement specific preparation, therefore a period of general focus (general non-specific movement preparation) was also taken into account.

While HV presented a relatively homogeneous group, the situation of chronic paraplegic patient is more complex. In the current study, we further categorized the SCI patient volunteers into two sub-groups, based on: the severity of paralysis and presence of chronic CNP pain. By combining patients with respect to different criteria, we investigated the influence of loss of motor control (HV vs. SCI), loss of sensation (CP/IP), and presence of CNP.

DISTINCTION BETWEEN HV AND SCI GROUPS

The largest differences in MRCP morphology were found between healthy and general mixed group of paraplegic patients during covert movements of feet in all phases of MRCP. It is interesting that significant difference was found even during the period of visual stimuli. Presenting a general warning sign produced significant difference between the groups (with a peak around 300–400 ms post-stimuli). This can be explained by the combined visual-motor nature of this potential, especially as the motor area is heavily involved in their generation but do not show much sensitivity to motor task parameters at this specific positive peak (Ulrich et al., 1998). It may be speculated that this positivity is generated by the increased firing rate of cortical neurons in motor areas, as in similar instruction delay experiments on primates that showed comparable delays after the cues (Cisek and Kalaska, 2004). Higher amplitude of the peak in SCI patients might be possibly related to higher effort/concentration in SCI patients expecting to imagine/attempt movement of a paralyzed limb. In SCI patients a motor potential in period $t > 0$ s had significantly higher negative peak with a rebound potential also called reafferent potential (Castro et al., 2013)- being delayed for several seconds. The amplitude of the rebound potential was also much lower in SCI group, which is explained by its relation to the kinesthetic feedback.

Statistically significant differences in MRCP morphology between these two groups were also found for motor imagery of the right hand, over electrode location C3, though to a smaller extent. This demonstrated the global influence of paralysis on modified EEG responses, and is in accordance with previous studies looking into either spontaneous (Tran et al., 2004; Boord et al., 2008; Vuckovic et al., 2014) or evoked brain activity (Vuckovic et al., 2014) in SCI patients. While the larger negativity during imagination of movement in paraplegic patients resembled the study by Lacourse (1999), there were many detailed differences that may originate from different cue type or EEG referencing.

DISTINCTION BETWEEN SCI SUBGROUPS

The analyzed group of patients was mixed with respect to the severity of paralysis and presence of chronic pain, therefore the results could not be conclusive. Therefore we further compared MRCP in patients with and without CNP. CNP is known to affects the activity of the motor cortex (Vuckovic et al., 2014), thus potentially influencing the morphology of MRCPs. Assuming that CNP is unrelated to the completeness of injury, patients with complete and incomplete injury were mixed. Analysis showed much smaller difference between patients with and without pain than between healthy and general SCI population.

The effect of CNP

It is known that CNP equally affects patients with complete and incomplete SCI (Siddall et al., 2003). A previous EEG study by Vuckovic et al. (2014), performed on the same group of volunteers, and the same experimental paradigm, demonstrated a difference in brain response between SCI patients with and without CNP, as well as between both groups of SCI patients and able-bodied volunteers. Those differences were wide spread over the sensory-motor cortex and were not restricted to imagination of paralyzed, "painful" part of the body. The study was based on ERD/ERS and was primarily interested in a time period after presentation of the directional cue, in a period $t = 0.4$–2 s.

The MRCP results in the current study are therefore not in accordance with the ERD/ERS analysis on the same patient group (Vuckovic et al., 2014). While paralysis resulted in reduced ERD, presence of CNP increased ERD. Therefore that study showed larger difference in cortical response between patients with and with no CNP than between patients with CNP and healthy subjects. The differences were pronounced within the first 2 s after presentation of the directional cue, while in the current study, the difference in MRCP morphology was significant in a short interval (0.3–0.6 s). This supports the idea of different origin of ERD and MRCP, which has been reported in the literature. The source of MRCP is related to the cerebellar-thalamus-cortical pathway (Babiloni et al., 1999; Rektor et al., 2001), while ERD is related to the thalamo-cortical feedback loops (Pfurtscheller and Lopes Da Silva, 1999). Since CNP is known to be not related to cerebellum activities (Vuckovic et al., 2014), the difference in the neurophysiological origin of MRCP and ERD supports the observed difference of MRCP and EDR with respect to the presence/absence of CNP.

The effect of the completeness of injury

Finally patients' MRCP were compared on the basis of the completeness of the injury, assuming that presence of CNP does not have a large effect on MRCP. For MRCP measured over Cz for motor imagery of feet, the largest difference was found in periods of both general preparation and covert movement execution in patients with complete injury.

Castro et al. (2013) compared MRCP in chronic paraplegic patients with complete injury and in healthy subjects during covert movement execution of left or right leg. Although in that study larger MRCP could be noticed over electrode locations C3, C4 and Cz, no difference was found when MRCP was averaged over all electrodes. In the current study, we analyzed only

electrode location where we expected largest MRCP. We also preprocessed the signal using large Laplacian filter that might have additionally enhances MRCP over these areas.

A general conclusion is that while both CNP and presence/absence of sensation affect the morphology of MRCP in paralyzed limb, the factor that most strongly influencs the MRCP is the lack of motor control, resulting in large difference between healthy subjects and general SCI group.

IMPLICATIONS FOR BCI-REHABILITATION

Results of MRCP classification supported the morphological analysis. In general the highest classification accuracy was found in the time windows which corresponded to the time windows of statistically significant difference between the groups. While classification accuracy between able-bodied group and patients exceeded 90%, classification between different patients groups was not higher than 65%. This further supports the idea that for MRCP-based BCI systems, paralysis is a factor that needs to be considered as it has a strong influence on the MRCP morphology. Therefore, the following issues should be seriously taken into consideration when developing MRCP-based BCI, especially cue-based BCI, for SCI patients.

Firstly, although the larger magnitude might probably improve the BCI performance in SCI patients, the prolonged rebound should be treated carefully with a long interval between trials. On the other hand, SCI PNP have weaker ERD than the able-bodied volunteers (Vuckovic et al., 2014), resulting in reduced BCI classification accuracy (Pfurtscheller et al., 2009). This implies that for SCI patients, BCI systems which relay on MRCP might have better classification accuracy, with greater consistency among patients.

Further, the lack of statistical difference of patient sub-groups with the distinct peaks in the corresponding *p*-value curves (lower panels of **Figure 2**) probably resulted from a much larger variability of MRCP in patients (both within and between subjects). This would affect the performance of BCI system for these patients.

Although almost no significant difference was found in the MRCP morphology between PWP and with no pain, chronic SCI patients with CNP might experience worsening of pain during prolonged MI practice (Gustin et al., 2010).

Finally, while it was the motor impairment (compared to the remaining sensory function or presence of pain) that had a considerable effect on the MRCP waveforms and can affect BCI performance, the clinical practice and therapy is by no means independent from these factors.

LIMITATIONS

The healthy group, which was comparable to the size of SCI subgroups, was not large. As the magnitude of MRCPs for hand was smaller than that of the foot task (see **Figure 3**), it would be better to have more subjects to increase statistical power of the analysis, so that statistical significance might be revealed in some cases where no significance was detected in the current analysis. Nevertheless, there were 60 trials for each type of task by each subject, so we had hundreds of segments (e.g., 480 for HV and 840 for SCI) for statistical comparison. In fact, we did find significance for HV vs. SCI for hand motor imagery (see **Figure 3**), but not for SCI subgroups. Given the very large *p*-value for PNP vs. PWP and CP vs. IP (only one peak is close to significance level), we believe the likelihood of missing potential significant differences was not large.

Other factors, besides the abnormal patterns in MRCP, could also contribute to the BCI design. One of these factors that was not discussed in this study is volitional inhibition (Logan, 1994), which refers to the cortical involvement of suppression of ongoing voluntary movements. Even though previous studies found that volitional inhibition activates motor cortexes (Coxon et al., 2006; Mirabella et al., 2011; Mattia et al., 2012), it does not attract much attention from the majority of BCI research community (Mirabella, 2012). Recently, Ifft et al. (2012) attempted to decode the volitional inhibition from brain signal, but there is still more work leaving for BCI researcher to dig information from overt movement as well as the volitional control (Fetz, 2007).

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Exploration of the neural correlates of cerebral palsy for sensorimotor BCI control

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Cerebral palsy (CP) includes a broad range of disorders, which can result in impairment of posture and movement control. Brain-computer interfaces (BCIs) have been proposed as assistive devices for individuals with CP. Better understanding of the neural processing underlying motor control in affected individuals could lead to more targeted BCI rehabilitation and treatment options. We have explored well-known neural correlates of movement, including event-related desynchronization (ERD), phase synchrony, and a recently-introduced measure of phase dynamics, in participants with CP and healthy control participants. Although present, significantly less ERD and phase locking were found in the group with CP. Additionally, inter-group differences in phase dynamics were also significant. Taken together these findings suggest that users with CP exhibit lower levels of motor cortex activation during motor imagery, as reflected in lower levels of ongoing mu suppression and less functional connectivity. These differences indicate that development of BCIs for individuals with CP may pose additional challenges beyond those faced in providing BCIs to healthy individuals.

Keywords: electroencephalogram (EEG), brain-computer interface (BCI), cerebral palsy, sensorimotor rhythm, event-related desynchronization (ERD), phase synchrony, phase dynamics

INTRODUCTION

Cerebral palsy (CP) can be a very debilitating life-long condition affecting activities of normal living. We explored a novel approach to the use of a brain-computer interface (BCI) to assist individuals with CP experiencing motor impairment. Given the difficulties people with CP have in using standard BCIs, we investigated alternative neural correlates of movement, which may allow better BCI control by this group.

CP describes a group of brain and nervous system disorders that can involve movement, learning, visual, and auditory perception, and cognitive processing (Miller, 2005). CP is caused by brain injury occurring pre- or peri-natally, or in the first 2 years of infancy (Holm, 1982; Odding et al., 2006). It may be induced by hypoxia to a particular brain area, or result from intracerebral hemorrhage, infection, head injury, or jaundice (Perlman, 1997).

CP can lead to difficulties in maintaining posture and coordinating movement. Problems include muscle tightening, abnormal gait, muscle weakness, tremors, spasms, and loss of coordination. Severity varies, and effects may be uni- or bilateral, involving upper, lower, or all limbs, occasionally resulting in almost complete paralysis (Krigger, 2006). Therefore, individuals with CP experience a range of challenges in their day-to-day lives for which they may require assistance.

BCIs offer a promising way of providing greater independence for individuals with CP (Wolpaw et al., 2002; Neuper et al., 2003; Millán et al., 2010; Sellers et al., 2010). BCIs base control of devices on direct recording and interpretation of brain activity. As such, they can enable control of a computer without activation of the efferent nervous system. BCIs can be used to control devices that could, for example, facilitate movement limited by weakness or poor coordination, or aid communication, establishing a direct, non-muscular, communication channel between a user and the environment (Wolpaw et al., 2002). Furthermore, although CP is a non-progressive condition, the associated symptoms may change over time as the individual's body grows and develops (Badawi et al., 2008). Such changes open the possibility of BCI-based neurofeedback approaches to alleviate motor impairments (Daly et al., 2013a). Moreover, it has been proposed that a motor imagery (MI) strategy could be beneficial in rehabilitation efforts to improve motor control in cases of cortical lesion induced movement impairments (reviewed by Zimmermann-Schlatter et al., 2008). Such an approach is encapsulated in a MI-BCI. MI-BCIs are based upon the detection of changes in sensorimotor rhythms (SMRs), oscillatory activity in the motor cortical regions (Pfurtscheller and Neuper, 2001), and have been suggested as effective communication devices for users with CP (Neuper et al., 2003).

One of the most common approaches to BCIs is based on event-related desynchronization (ERD), which is a modulation in cortical electrical activity before, during, and after attempted

execution, or imagination, of active or passive movement, manifested in the electroencephalogram (EEG) (Pfurtscheller and Lopes da Silva, 1999; Müller-Putz et al., 2003, 2007), magnetoencephalogram and electrocorticogram (Hinterberger et al., 2008; Foldes, 2011). The corresponding representation area in the motor cortex exhibits suppression of on-going oscillatory activity in the alpha (8–13 Hz) and beta (13–30 Hz) frequency bands (Niedermeyer, 1999; Pfurtscheller and Lopes da Silva, 1999). After movement cessation, beta oscillatory activity increases over baseline event-related synchronization (ERS) then returns to baseline activity. This process is considered to correspond either to a motor cortex inhibition or a sensory reafference (Baker, 2007; Müller-Putz et al., 2007). Mu and beta activity are modified by limb movement and MI (Pfurtscheller et al., 1997; Neuper et al., 1999).

Despite promising results with ERD-based BCI control in healthy populations, previous studies have shown that users with CP were not able to control an MI-BCI based upon ERD/S at comparable accuracy levels (Neuper et al., 2003; Daly et al., 2013a). However, MI-BCIs offer a number of advantages over other BCIs, including not requiring any executed movement, e.g., eye gaze, which a number of other BCIs [such as steady state visual evoked potential (SSVEP)- and event related potential (ERP)-based BCIs] require. Furthermore, they are intuitive, and in a pilot exercise, participants reported using such BCIs to be enjoyable (Daly et al., 2013b), increasing motivation, which is advantageous when BCIs are being employed for rehabilitation purposes. We therefore investigated differences in SMR activity in participants with CP and healthy participants in order to explain the diminished performance in users with CP, as well as to explore other neural correlates of MI, which may be more useful for controlling BCIs in this group.

More recently, a new way of interpreting how the brain may process information, based on interactions between different brain areas rather than solely on their activations, has been gaining prominence in cognitive neuroscience. Human and animal studies indicate that transient episodes of long- and short-range phase synchrony, between distant and adjacent cerebral areas, as measured by pair-wise interactions between electrodes at micro- and/or macro spacings, correspond to perceptual and cognitive processes (Varela et al., 2001). Such synchrony has been proposed to underpin cognitive acts through the transient formation and dissolution of neural assemblies (Varela et al., 2001). The phase locking value (PLV), as introduced in Lachaux et al. (1999), provides a method for quantifying the degree of phase synchrony in a particular frequency band between different time series of electrical brain activity, such as recorded from EEG electrodes at different scalp locations. In contrast to coherence measurement, the PLV is strictly sensitive to the phase and not to the amplitude of the signals (Varela et al., 2001; Brunner et al., 2006). A PLV close to 0 indicates no synchrony, while a value close to 1 indicates perfect synchrony of the two compared time series at that point.

Changes in coordination of activity through timing have been identified in motor cortex activity during movement (Meinecke et al., 2005; Sweeney-Reed and Nasuto, 2009). Local phase synchrony in the motor cortex alpha band has been found to increase prior to movement, decreasing at movement, then increasing again afterwards in healthy participants (Sweeney-Reed and Nasuto, 2009). These electrical activity changes are also potential candidates for controlling an MI-BCI.

Furthermore, the temporal dynamics of synchrony exhibit changes during MI tasks (Daly et al., 2011). We recently proposed an approach to modeling phase synchronization dynamics in the EEG during a motor task in healthy individuals (Daly et al., 2013c). Differences in temporal dynamics of phase relations between participant groups could indicate a difference in timing of cortical integration resulting from CP lesions, offering another approach to BCI control.

A number of questions arise. It is currently unknown how CP-induced motor-cortical lesions affect ERD strength, MI efficacy, or other SMR-related activity such as phase relationships, despite the potential benefits to CP sufferers from the use of SMR activity to control a BCI. Crucial to the development of effective BCIs for this group is determination of whether CP-related impairment also results in alteration of the electrophysiological patterns usually detected during MI. The question is particularly important, as individuals with CP are among those who stand to benefit significantly from BCI use.

We therefore had two goals. First, we assessed how motor cortex SMR activity differs in individuals with CP compared with healthy individuals, in order to identify a useful approach to BCI control in users with CP. Second, we sought to further our understanding of the motor impairments in CP through detailed examination of electrical activity in the motor cortex during MI.

MATERIALS AND METHODS

Participants with CP and healthy controls attempted to control a BCI using MI. Institutional review board ethical approval was obtained prior to all measurements. We first provide details of the EEG recording and BCI paradigm, before describing the analysis methods and inter-group comparisons.

HEALTHY PARTICIPANTS

The first dataset was from 12 able-bodied BCI-naïve volunteers (5 female and 7 male, median age 26 $\pm$ 3.0 years). Details of these participants are listed in **Table 1**.

Table 1 | Summary of the healthy participants.

Participant	Age	Gender
1	32	F
2	21	M
3	26	F
4	27	M
5	26	M
6	22	F
7	28	F
8	26	M
9	28	M
10	26	M
11	22	M
12	25	F

Gender is indicated by either M (male) or F (female).

These data were recorded in a cue-guided, auto-calibrating and adaptive ERD-based BCI paradigm (see Faller et al., 2012 for details). EEG was recorded from electrodes FC3, FCz, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CPz, and CP4 via a g.GAMMAsys active electrode system along with a g.USBamp amplifier (g.tec, Guger Technologies OEG, Graz, Austria).

In this study only EEG from the first training session was used to remove bias due to practice. In every trial, we displayed a fixation cross over the entire trial duration. Between 1.5 and 2.75 s, a visual cue indicated the required task. The participants were instructed to perform kinesthetic MI of their right hand (condition 1) or both feet (condition 2) from the time the cue appeared on the screen until the time the cross disappeared (**Figure 1A**).

The system collected data offline until 10 trials were available for each class (∼3.5 min). After enough trials had been recorded during the training phase, online positive reinforcement regarding the strength of the mental activity was provided to the participants for each trial during data measurement. As only trials from the training phase were considered in this work, we do not detail this here. Further details may be found in Faller et al. (2012).

It is important to note that one of the aims of this work was to investigate motor control processes during BCI control. BCI control is typically based on either a small number of averaged trials or single trials. Indeed results identified from averaging across a larger number of trials could be misleading when applied to BCI.

PARTICIPANTS WITH CP

The second dataset was recorded from 14 BCI-naïve volunteers with CP (7 female and 7 male, median age 36 ± 11 years). All participants exhibited upper limb disorders and 10 participants also exhibited lower limb disorders. Details of these participants are provided in **Table 2**.

EEG was recorded from electrodes AFz, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, PO3, POz, PO4, O1, Oz, and O2 via a g.GAMMAsys active electrode system along with a g.USBamp amplifier (g.tec, Guger Technologies OEG, Graz, Austria). Further details on the participants are reported elsewhere (Daly et al., 2013a).

A similar paradigm to that applied with the able-bodied participants was used. A cue-guided, auto-calibrating and adaptive SMR BCI paradigm was optimized for disabled users. The timing of the trials was adjusted based upon requests made by participants with CP, in a prior pilot study, for a longer MI period (see Daly et al., 2013a for details).

We presented a fixation cross from 0 to 1.5 s. From 1.5 to 3.5 s, a visual cue indicated the required task. From 3.5 to 8 s the system again displayed the fixation cross. The participants were instructed to perform four mental tasks, of which only kinesthetic MI of either hand (condition 1) or both feet (condition 2) were used for this analysis (see **Figure 1B**).

After the first auto-calibration, the system displayed feedback in the form of a bar, as with the control participants, from 3.5 to 8 s. Data were collected offline for the four conditions until a sufficient number of artifact-free trials were gathered for accurate estimation of the class boundaries. Thus, different numbers of trials were gathered per participant. Further details are provided in Daly et al. (2013a).

In this study, as with the control group, only EEG from the training period was used, to remove bias due to practice. Note that the length of the training period differed between participants, as some participants required more repetitions than others before sufficient class separation could be obtained by the classifier. Details on the feedback provided after the training phase may be found in Daly et al. (2013a).

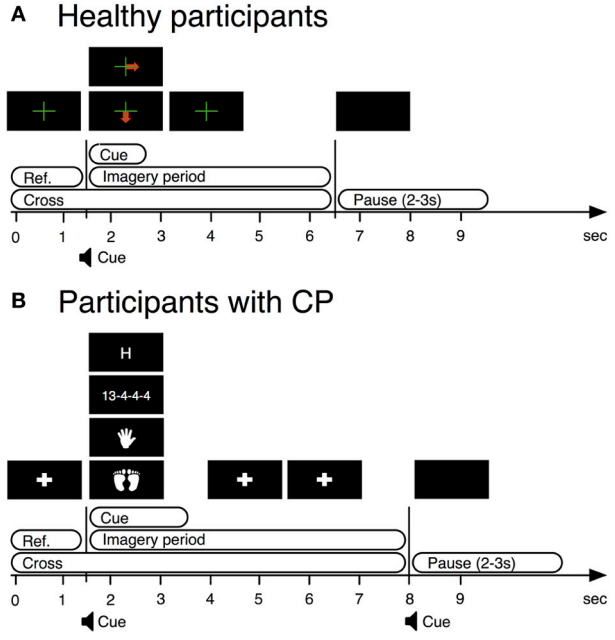

FIGURE 1 | BCI paradigms used in training stages of BCI operation by both users with CP and healthy users. (A) BCI paradigm used with healthy participants. **(B)** BCI paradigm used with participants with cerebral palsy.

Table 2 | Summary of the participants with CP.

Participant	Age	Gender	Orthopedic disorders
1	53	M	LLD, ULD
2	36	M	LLD, ULD
3	52	F	LLD
4	22	M	LLD, ULD
5	32	M	LLD
6	20	F	LLD, ULD
7	34	M	LLD, ULD
8	58	F	LLD
9	32	F	LLD
10	36	F	LLD, ULD
11	38	M	LLD, ULD
12	36	F	LLD, ULD
13	37	M	LLD, ULD
14	31	F	LLD, ULD

Gender is indicated by either M (male) or F (female). Orthopedic disorders are denoted by codes indicating lower limb disorders (LLD) or upper limb disorders (ULD).

PRE-PROCESSING

EEG from nine channels positioned over the motor cortex and common to the recording montage used with both participant groups was used (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, and CP4). The data were then re-referenced to a common average reference (CAR) scheme before segmentation into trials.

Trials containing artifacts were then identified as any trial for which the amplitude exceeded $\pm 80\,\mu V$. These trials were excluded from subsequent analysis. From the healthy users 2.58 ($\pm$2.72) trials were removed and from the users with CP 8.07 ($\pm$7.49) trials were removed.

As we were only interested in trials relating to the 2 MI tasks common to both groups, this leaves a total of 17.33 ($\pm$2.77) trials remaining for healthy users and 19.92 ($\pm$7.49) trials remaining for users with CP.

We focused on four frequency bands of interest in subsequent processing steps. These were the alpha (8–13 Hz), lower beta (13–16 Hz), mid beta (16–20 Hz), and upper beta (20–30 Hz) frequency bands.

BANDPOWER FEATURES

Band-powers (BP) were calculated for all channels as the root mean squared amplitude of the EEG filtered into the frequency bands of interest. These frequency bands were chosen as they are well-known to contain the ERD/S response observed during motor planning and execution/imagery (Pfurtscheller and Lopes da Silva, 1999). The data were then baselined; the mean BP amplitude in the 1.5 s prior to cue appearance was subtracted from the data.

Our aim was to derive a representative BP response from the EEG for the participants with CP, in order to examine potential differences to healthy participants. Even within a specific CP subtype, CP inherently has significant variability, as lesions can occur at different locations or take different forms such as malformations, periventricular lesions or cortico-subcortical lesions (Wu et al., 2006; Korzeniewski et al., 2008). We therefore averaged the BP of the nine CAR channels described above to attempt to correct for inter-participant differences in spatial locations of greatest ERD/S manifestation.

Additionally, baseline BP in the 1.5 s pre-cue baseline period was also compared between groups.

PHASE LOCKING VALUE (PLV)

Following bandpass filtering to provide a narrow band signal, PLVs between channel pairs were calculated as per Lachaux et al. (1999). We filtered the channels into the four frequency bands of interest. We then extracted the instantaneous phase from each trial using the Hilbert transform and calculated the PLV pair-wise for all possible channel combinations according to the following formula (Lachaux et al., 1999)

$$\mathrm{PLV_t} = \frac{1}{\mathrm{N}} \left| \sum\nolimits_{\mathrm{n}=1}^{\mathrm{N}} \exp(\mathrm{j}\theta(\mathrm{t},\mathrm{n})) \right|,$$

where N denotes the number of trials to average, t denotes the time point in the time series, and θ(t,n) denotes the phase difference between the two time series. The PLVs for all possible pairwise combinations were then averaged as per the approach taken in Sweeney-Reed et al. (2012).

Additionally, PLVs between the primary motor cortex (M1) and the supplementary motor area (SMA) were estimated by measuring the mean PLV between channels FPz-C3, FPz-Cz, and FPz-C4. This was based upon observed strong PLV between M1 and the SMA during MI-BCI control (Wang et al., 2006).

PHASE DYNAMICS

The temporal dynamics of the phase of the EEG across multiple EEG channels were compared using the method described in Daly et al. (2013c). First, the phase values from the preprocessed multivariate EEG time series from the channels over the motor cortex (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, and CP4) were used to define a relative phase vector by taking their phase relative to the average phase on a set of reference channels. These reference channels were chosen to minimize the effect of specific phase dynamics on one channel biasing the results and are symmetrically arranged about the midline. Formally,

$$\Phi_{\mathrm{i}}\,(\mathrm{t}) = \theta_{\mathrm{i}}\,(\mathrm{t}) - \theta_{\mathrm{R}}(\mathrm{t}),$$

where $\theta_{\mathrm{i}}(\mathrm{t})$ denotes the phase on channel i at time t and $\theta_{\mathrm{R}}(\mathrm{t})$ denotes the phase on a reference channel R at time t. The following four channels were used as references FC3, FC4, CP3, and CP4. These were chosen as they surround the channels most often associated with MI (C3, Cz, and C4).

A relative phase pattern vector was then defined as

$$\Upsilon\,(\mathrm{t}) = (\Phi_1\,(\mathrm{t})\,, \ldots, \Phi_{\mathrm{N}}\,(\mathrm{t})\,),$$

where N denotes the number of channels for which relative phase Φ_{i} was calculated.

The relative phase pattern vector characterizes the phase across the multivariate time series at a given moment in time. Thus, its temporal evolution is informative about the temporal dynamics of phase across the motor cortex.

The time series of relative phase patterns were then segmented into regions of phase stability. This was done via the Instantaneous Instability Index (III) (Ito et al., 2007) of the relative phase pattern vectors, which is defined as

$$\mathrm{I}\,(\mathrm{t}) = \sqrt{\sum\nolimits_{\mathrm{i}=1}^{\mathrm{N}} \mathrm{d_i}(\mathrm{t})^2},$$

with

$$\mathrm{d_i}\,(\mathrm{t}) = \frac{1}{\mathrm{N}} \sum\nolimits_{\mathrm{h}=1}^{\mathrm{N}} \{1 - \cos\,(\Phi_{\mathrm{i}}\,(\mathrm{t}) - \Phi_{\mathrm{h}}\,(\mathrm{t})\,)\,\}.$$

A period of phase stability may be defined as a period for which I falls below a certain percentile of its magnitude values; the fiftieth percentile—as used in Ito et al. (2007)—was used in this work. A Global Phase Synchronization (GPS) pattern vector was then defined across each of the periods of synchronization. Formally,

$$\mathrm{p^g} = (\Xi_1^{\mathrm{g}}, \ldots, \Xi_{\mathrm{N}}^{\mathrm{g}}),$$

defines the GPS pattern vector, where

$$\Xi_i^g = \tan^{-1} \frac{\sum_{t \in l^g} \sin \Phi_i(t)}{\sum_{t \in l^g} \cos \Phi_i(t)},$$

and where l^g denotes the gth GPS episode, with $1 \leq g \leq M$ and M is equal to the number of GPS episodes. Thus, the vector p^g gives the average phase pattern during a single episode of GPS.

The entire series of phase pattern vectors p^g was then clustered and labeled via a K-means clustering approach to produce a labeled GPS time-series, s^g. In this work $K = 6$, based upon the choice made in Ito et al. (2007) and Daly et al. (2013c).

The temporal dynamics of phase synchronization patterns (the labeled GPS time-series) were characterized by a Hidden Markov model (HMM) which attempted to capture the temporal dynamics of the process by assuming an underlying stochastic system modeled by a series of state transitions. Each of the k states within the HMM can generate observables, which comprise the values taken by the labeled GPS time-series.

HMMs may be used to model and classify the temporal dynamics of phase pattern vectors. Initial parameters were drawn from uniform distributions. Further details of how this may be done are reported elsewhere (Daly et al., 2013c). In this work the number of states in the HMM was determined by application of a summation of Akaike's information criterion and Bayesian information criteria (AIC + BIC) (Visser et al., 2002). The HMM toolbox provided by Murphy (1998) was chosen for implementation due to its low computational cost.

COMPARISON

Stepwise regressions were calculated with mean BP strengths and PLVs over all trials in the MI period used as the criteria. The time series of relative BPs and PLVs were first segmented into time windows of length 2 s from 0 s relative to the cross onset to 8 s. Thus, four time segments were created (0–2, 2–4, 4–6, and 6–8 s) and BP strengths and PLV values averaged over these time segments.

The predictors were group (healthy users vs. users with CP), age, gender, and number of artifact-free trials completed by each participant and included in the analysis. Separate regressions were performed for the classes hand and feet MI with mean ERD/S and PLV strengths in the alpha and beta bands.

Comparisons were made across four frequency bands and four time segments. It may be argued that a Bonferroni correction is required. However, subsequent time segments are not independent of one another, which is assumed by Bonferroni correction. Additionally, the frequency bands investigated were selected based upon their known involvement in motor-related activity (Pfurtscheller et al., 1997). Therefore, because of the lack of independence between time segments, and because we expect motor related responses at many of the investigated frequencies, we list all comparisons significant at $p < 0.05$ (uncorrected).

In order to assess the reliability of differing phase dynamics to differentiate between user groups, HMMs were trained and applied to classify the mean BP and PLV trials from each participant into either users with CP or healthy users in a leave-one-out train and validation scheme. This was done independently for the hand and feet MI conditions. Statistical significance of the resulting accuracy was then assessed against the null hypothesis of equal probability of each class label being assigned.

Additionally, to determine whether the HMM classification result was determined by the user group (users with CP vs. healthy users), or some other factor (e.g., age), stepwise regressions were calculated. The log-likelihood ratio between the two groups was entered as the criterion. The predictors were group (healthy users vs. users with CP), age, gender, and the number of artifact-free trials completed by each of the participants. Separate regressions were performed for the classes hand and feet MI.

Note, *t*-testing was used for *post-hoc* testing and assumes normality of each tested distribution. To check for this a one sample Kolmogorov–Smirnov test for normality was performed prior to each *post-hoc t*-test reported throughout this work.

RESULTS

During periods of MI both healthy BCI users and BCI users with CP exhibited ERD/S changes from baseline in the alpha and beta frequency bands. These were accompanied by increases over baseline in the degree of observed PLV. Background PLV levels were also observed to be higher in participants with CP compared to healthy participants. Finally, significant differences were observed in phase dynamics between participant groups, with healthy participants exhibiting greater levels of inter-channel phase differences than participants with CP. These findings are summarized in **Table 3** and detailed in the following sections.

SENSORIMOTOR RHYTHM ACTIVITY

Results are summarized in **Table 4**. In the alpha frequency band (8–13 Hz) larger ERDs were found for hand MI in healthy participants. A significant effect of group (healthy users vs. users with CP) was found for the hand MI task in time segments

Table 3 | Summary of key findings.

	Healthy	CP
Baseline PLV	<	
Relative PLV	>	
Relative ERD/S	>	
III dynamics	>	

Table 4 | Summary of significant ERD/S findings.

MI: hand/feet	Group with greater ERD	Frequency	Time (s)	Stepwise regression r^2-value	*Post-hoc t*-test *p*-value
Hand	Healthy	Alpha	4–6	0.148	=0.034
Hand	Healthy	Alpha	6–8	0.180	=0.033
Hand	Healthy	Mid beta	4–6	0.156	=0.048
Hand	Healthy	Mid beta	6–8	0.176	=0.043
Feet	Healthy	Mid beta	4–6	0.239	=0.004
Feet	Healthy	Mid beta	6–8	0.231	=0.017
Hand	Healthy	High beta	4–6	0.310	=0.005

4–6 s ($r^2 = 0.148$; $p = 0.0473$) and 6–8 s ($r^2 = 0.180$; $p = 0.0274$). Note, r^2 denotes the root mean squared fit of the model.

Post-hoc t-tests revealed a significantly larger (more negative) BP reduction in healthy users than users with CP (i.e., MI-related ERD was significantly less in the CP group) ($p = 0.034$ and $p = 0.033$). No other significant effects were observed in the alpha frequency band.

In all instances of *post-hoc* testing the test failed to reject the null hypothesis of normality ($p > 0.05$ and $p > 0.01$).

In the mid beta band (16–20 Hz) significantly larger ERDs were observed in healthy participants from 4 s onwards during both hand and feet MI. A significant effect of group was found during hand MI between 4 and 6 s ($r^2 = 0.156$; $p = 0.042$). *Post-hoc* testing (*t*-test) revealed a significantly greater ERD (more negative relative BP) in healthy users ($p = 0.048$). Additionally, between 6 and 8 s during hand MI, there was a significant effect of group ($r^2 = 0.176$; $p = 0.011$). *Post-hoc* testing revealed a significantly greater ERD (more negative BP) in healthy users. Between 4–6 s ($r^2 = 0.239$; $p = 0.009$) and 6–8 s ($r^2 = 0.231$; $p = 0.011$) significant effects of group were observed, with *post-hoc t*-tests revealing significantly more ERD (negative BP) in healthy users ($p = 0.004$) than users with CP ($p = 0.017$).

In the upper beta frequency band (20–30 Hz) larger ERD was observed during hand MI in healthy participants. A significant effect of group was observed during hand MI between 4 and 6 s ($r^2 = 0.310$; $p = 0.002$). A *post-hoc t*-test again revealed significantly more ERD (negative relative BP) in healthy users ($p = 0.005$). Note, no other significant effects of any predictors were observed in any frequency band. Also of note, is the observation that the lower beta frequency band (13–16 Hz) contained no significant effects of any independent variable within any time segments.

An example of mean BPs in the mid beta frequency band during hand MI tasks for each participant group is illustrated in **Figure 2**. Note the large negative BP fluctuation exhibited by healthy users when compared to users with CP.

Significant differences were observed in the 1.5 s baseline period, with significant effects of group in most frequency bands and classes (hand-alpha: $r^2 = 0.351$; $p = 0.002$, foot-alpha: $r^2 = 0.286$; $p = 0.007$, hand-lower-beta: $r^2 = 0.235$; $p = 0.022$, hand-mid-beta: $r^2 = 0.275$; $p < 0.001$, foot-mid-beta: $r^2 = 0.236$; $p = 0.005$, hand-upper-beta: $r^2 = 0.269$; $p < 0.001$, foot-upper-beta: $r^2 = 0.264$ $p = 0.001$). In each case *post-hoc* testing (*t*-test) revealed significantly larger baseline (background) BP recorded from individuals with CP.

PHASE LOCKING VALUES

Results for PLVs are summarized in **Table 5**.

In the alpha frequency band a significant effect of group was observed during hand MI between 4–6 s ($r^2 = 0.268$; $p = 0.006$) and 6–8 s ($r^2 = 0.364$; $p = 0.001$). *Post-hoc* tests (*t*-tests) revealed relative PLV values to be significantly higher in healthy users ($p = 0.013$) compared to users with CP ($p < 0.001$).

When considering the PLVs between M1 and the SMA a significant effect of group was observed during hand MI between 4–6 s ($r^2 = 0.167$; $p = 0.034$) and 6–8 s ($r^2 = 0.232$; $p = 0.011$). *Post-hoc* testing revealed a significantly higher level of M1-SMA PLV in healthy users ($p = 0.034$ and $p = 0.009$). Additionally, a significant effect of gender was observed during feet MI between 0 and 2 s ($r^2 = 0.148$; $p = 0.047$). *Post-hoc* testing revealed significantly higher M1-SMA PLV for female participants ($p = 0.029$).

In the lower beta frequency band a significant effect of group was observed in the time window 6–8 s during hand MI ($r^2 = 0.239$; $p = 0.009$) and during feet MI ($r^2 = 0.183$; $p = 0.026$). A *post-hoc t*-test revealed a significant increase in PLVs in healthy users ($p = 0.012$ and $p = 0.009$). A significant effect of group was also observed for the M1-SMA PLV in the lower beta band during hand MI between 6 and 8 s ($r^2 = 0.225$; $p = 0.012$). *Post-hoc* testing revealed a larger PLV in healthy participants ($p = 0.016$).

In the mid beta frequency band a significant effect of Group was observed during hand MI in time segments 4–6 s ($r^2 = 0.336$; $p = 0.001$) and 6–8 s ($r^2 = 0.347$; $p < 0.001$). *Post-hoc t*-tests again revealed significantly larger PLVs in healthy users ($p =$

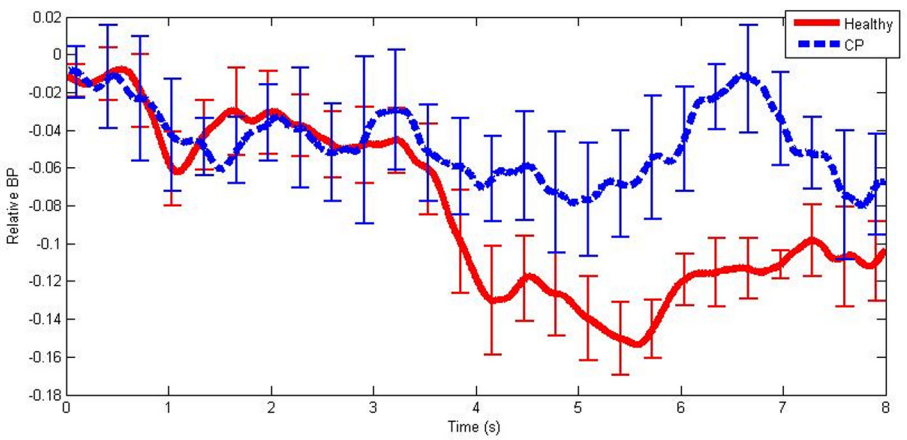

FIGURE 2 | An example of mean band-power differences from baseline from healthy users and users with CP in the mid beta frequency band during hand MI. The error bars illustrate ±1 standard deviation from the mean.

0.006 and $p = 0.004$). During feet MI significant effects of group were also observed during time segments 4–6 s ($r^2 = 0.202$; $p = 0.019$) and 6–8 s ($r^2 = 0.376$; $p < 0.001$). *Post-hoc* t-tests revealed significantly larger PLVs in healthy users compared to users with CP ($p = 0.025$ and $p = 0.015$).

Table 5 | Summary of significant PLV findings.

MI: hand/feet Region: MC/M1-SMA	Group with greater PLV	Frequency	Time (s)	Stepwise regression r^2-value	*Post-hoc* t-test p-value
Hand, MC	Healthy	Alpha	4–6	0.268	=0.013
Hand, MC	Healthy	Alpha	6–8	0.364	=0.001
Hand, M1-SMA	Healthy	Alpha	4–6	0.167	=0.034
Hand, M1-SMA	Healthy	Alpha	6–8	0.232	=0.009
Hand, MC	Healthy	Lower beta	6–8	0.239	=0.012
Feet, MC	Healthy	Lower beta	6–8	0.183	=0.009
Hand, M1-SMA	Healthy	Lower beta	6–8	0.225	=0.012
Hand, MC	Healthy	Mid beta	4–6	0.336	=0.006
Hand, MC	Healthy	Mid beta	6–8	0.347	=0.004
Feet, MC	Healthy	Mid beta	4–6	0.202	=0.025
Feet, MC	Healthy	Mid beta	6–8	0.376	=0.015
Hand, M1-SMA	Healthy	Mid beta	6–8	0.197	=0.014
Feet, M1-SMA	Healthy	Mid beta	4–6	0.196	=0.036
Feet, M1-SMA	Healthy	Mid beta	6–8	0.266	=0.011
Hand, MC	Healthy	Upper beta	0–2	0.214	=0.004
Hand, MC	Healthy	Upper beta	2–4	0.268	=0.003
Hand, MC	Healthy	Upper beta	4–6	0.511	<0.001
Hand, MC	Healthy	Upper beta	6–8	0.399	=0.002
Feet, MC	Healthy	Upper beta	4–6	0.169	=0.021
Hand, M1-SMA	Healthy	Upper beta	4–6	0.341	=0.005
Hand, M1-SMA	Healthy	Upper beta	6–8	0.303	=0.009

Region denotes the region of the motor cortex considered where MC denotes the whole motor cortex and M1-SMA denotes PLVs between the M1 and SMA regions.

When considering the PLV between M1 and the SMA in the mid beta band a significant effect of group was observed during hand MI between 6–8 s ($r^2 = 0.197$; $p = 0.001$) and during feet MI between 4 and 6 s ($r^2 = 0.196$; $p = 0.021$) and 6–8 s ($r^2 = 0.266$; $p = 0.006$). *Post-hoc* t-tests revealed significantly larger PLVs in healthy users compared to users with CP ($p = 0.014$; $p = 0.036$; $p = 0.011$). Additionally, significant effects of gender were observed during hand MI between 0 and 2 s ($r^2 = 0.191$; $p = 0.023$), with a *post-hoc* t-test revealing significantly larger PLVs in female users ($p = 0.027$).

In the upper beta frequency band, significant effects of group were observed in time segments 0–2 s ($r^2 = 0.214$; $p = 0.015$), 2–4 s ($r^2 = 0.268$; $p = 0.006$), 4–6 s ($r^2 = 0.511$; $p < 0.001$), and 6–8 s ($r^2 = 0.399$; $p < 0.001$) during hand MI. *Post-hoc* t-tests revealed that in each case there were significantly larger PLVs in the healthy users than in the users with CP ($p = 0.004$, $p = 0.003$, $p < 0.001$, and $p = 0.002$). Additionally, during feet MI a significant effect of user age was observed in the time segment 0–2 s ($r^2 = 0.195$; $p = 0.021$), with *post-hoc* testing (correlation) revealing a significant negative correlation with PLV strength decreasing with increasing age ($r = -0.442$; $p = 0.021$). Finally, during feet MI significant effects of group ($r^2 = 0.169$; $p = 0.009$) and participant gender ($r^2 = 0.364$; $p = 0.012$) were observed in the time segment 4–6 s, with *post-hoc* t-tests revealing larger PLVs in healthy users ($p = 0.021$) and larger PLVs in female users ($p = 0.032$).

Significant effects of group were also found for PLVs between M1 and the SMA in the upper beta band during hand MI between 4–6 s ($r^2 = 0.341$; $p < 0.001$) and 6–8 s ($r^2 = 0.303$; $p = 0.003$), with *post-hoc* t-tests revealing larger PLVs in healthy users ($p = 0.005$ and $p = 0.009$). Additionally, a significant effect of gender was observed during feet MI between 4 and 6 s ($r^2 = 0.212$; $p = 0.016$), with a *post-hoc* t-test revealing a larger PLV in female users ($p = 0.040$).

An example of mean relative PLVs in the mid beta frequency band during hand MI is illustrated in **Figure 3**. Note that there

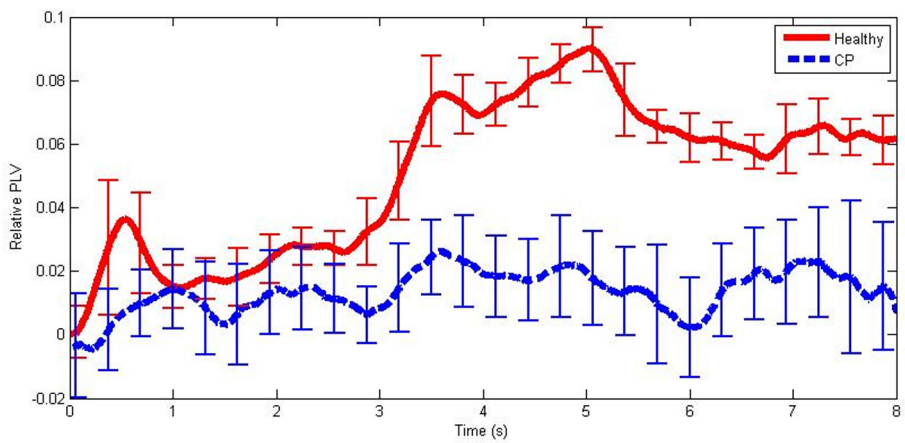

FIGURE 3 | An example of mean PLV differences from baseline from healthy users and users with CP in the mid beta frequency band during hand MI. The error bars illustrate ±1 standard deviation from the mean.

was a large increase in PLV in the healthy user group and only a very small increase in the group of users with CP.

PHASE DYNAMICS

Phase dynamics may be observed in the time series of III values. An example is illustrated in **Figure 4**. Note that healthy users exhibited greater III levels than users with CP. The higher levels indicate a greater amount of instability in the inter-channel phase differences in the healthy individuals.

Users may be differentiated by their group (either users with CP or healthy users) with an accuracy of 0.7143 ($p < 0.05$) for the hand MI condition and 0.7500 ($p < 0.05$) for the feet MI condition. Thus, a significant difference was observed in phase dynamics between users with CP and healthy users during both MI tasks.

The results of the stepwise regressions revealed a significant effect of group ($r^2 = 0.168$; $p = 0.046$) for hand MI.

Additionally, a significant effect of group ($r^2 = 0.179$; $p = 0.039$) was also revealed for feet MI with no significant effects of any other predictors. This result indicates that the difference in log likelihoods of the phase dynamics of each user being generated by one or other of the HMMs was determined by the users' group rather than other potential factors such as their age. This result, therefore, further confirms a significant difference in phase dynamics between users with CP and healthy users.

DISCUSSION

Individuals with CP exhibited statistically significantly smaller ERD strengths and PLVs in channels recorded over the motor cortex than healthy individuals while performing two common BCI control tasks: hand MI and feet MI. Significant differences were observed most often between 4 and 8 s relative to fixation cross presentation time. There was also a larger BP in the baseline period in individuals with CP. Additionally, analogous differences were also observed in motor cortex PLV strengths and PLV strengths between the primary motor cortex (M1) and the SMA.

The observed differences were most frequently explained by the participants' group (whether they have CP or not), as compared to differences in age, numbers of trials performed, or gender, which only sporadically explained the observed differences. Furthermore, a significant difference was also observed in the phase dynamics exhibited by each participant group, with individuals with CP exhibiting smaller differences in moment-to-moment phase stability.

It is important to consider the time course of the trial when discussing these results. All the trials included for analysis are from the training runs for both the healthy users and the users with CP. During these runs, no feedback was provided to the users. Hence, it was not clear to users at which point MI should cease. This is reflected in the long periods of observed MI which extend up to 8 s from fixation cross presentation time.

The lesser degree of ERD coupled with higher baseline BP activity suggests impairment of motor cortical engagement during attempted motor control tasks in individuals with CP, resulting in reduced levels of suppression of the ongoing alpha and beta frequencies and different temporal dynamics. The latter was indicated by reduced short-range synchronization of motor cortex activity and differing rates of phase state transitions. High levels of local phase synchrony in motor areas have been shown to precede movement in healthy participants, possibly due to a participant involved in a motor-related task being in a continual state of readiness to move, followed by a phase-scattering which has been interpreted as preparation for the selection of the particular neural assembly required for the selected movement (Sweeney-Reed and Nasuto, 2009). The present results indicate that such a state of preparedness is reduced or absent in participants with CP, and we suggest that this may be a result of inadequate development of the ability to form relevant functional connectivity patterns during early developmental stages. Additionally, the higher levels of background activity in the alpha and beta frequency bands (as indicated via the differences in baseline activity) may indicate less motor cortical localisation and specialization in individuals with CP.

The smaller III fluctuations in the group of participants with CP are an interesting observation. III reflects the number of transitions between phase microstates (Ito et al., 2007), which represent short lasting periods of stability in the electrical activity in the brain. Such electrical activity is thought to follow a pattern of chaotic itinerancy in which the trajectory of phase activity wanders through a landscape of ruined attractors (Ito et al., 2007). A smaller level of III fluctuation therefore corresponds to longer time periods spent at each localized attractor and a potentially less reactive set of dynamics. This may be indicative of a more diffuse (unstructured) mode of inter-cortical communication in individuals with CP.

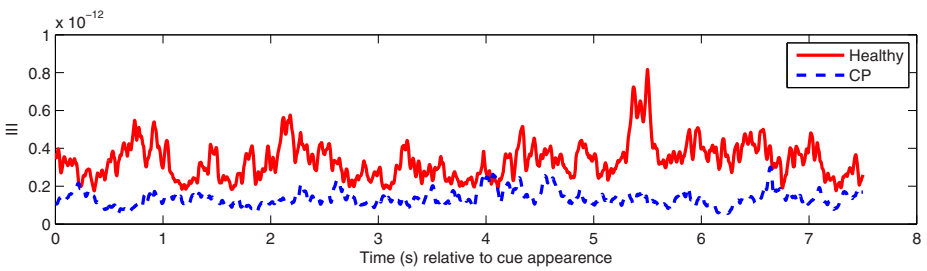

FIGURE 4 | An example of mean III time series over participants in the alpha (8–13 Hz) frequency band from healthy users and users with CP during hand MI.

A number of factors could explain why such differences were observed between users with CP and healthy users. One possibility is that the fetal brain damage experienced by individuals with CP prevents the learning of reliable motor control in the early developmental stages of childhood. As such, individuals with CP may experience more difficulty acquiring reliable control of their motor functions (Palisano et al., 1997) and, hence be unable to reliably produce the associated ERD responses.

It has been shown elsewhere that, in addition to impairment in motor planning, individuals with CP also exhibit impairment in MI as measured via rotation-related negativity by Parson's hand rotation paradigm (Crajé et al., 2010; Van Elk et al., 2010). As there is a known relationship between efficacy at hand mental rotation and ERD strength (Chen et al., 2013), it is reasonable to speculate that there may, therefore, be a relationship between CP-related impairment and ERD strength.

In contrast, individuals with severe stroke lesion induced impairments are seen to exhibit larger ERD/S strengths (Kaiser et al., 2012). Furthermore, the ERD strength may increase in the non-lesioned hemisphere (possibly as a compensatory neuroplastic change). While it is reasonable to hypothesize that lesions occurring in the fetal brain or during infancy will also induce changes in ERD strength, the lack of a compensatory increase in ERD strength elsewhere in the motor cortex may be, potentially, explained by recruitment of those cortical areas for other functions.

Additionally, post-stroke the ERD/S strength may reflect a re-learning process as the individual attempts to recruit other cortical areas to re-learn actions familiar pre-stroke. In the case of individuals with CP, such re-learning may not be possible, as the impairment was present from childhood, and motor cortical pathways are either damaged or have since been recruited for other tasks via neuroplastic processes.

Another factor that may explain the differences between individuals with CP and post-stroke individuals could relate to differences in learning processes. It has been reported that children with CP exhibit significantly slower rates of learning motor tasks than aged-matched healthy children (Hung and Gordon, 2013). Learning to use a MI-BCI may be described as akin to a motor learning task. Therefore, the lower ERD responses observed by individuals using our BCI may be a result of a slower learning process. Given further training, it is possible that individuals with CP may eventually learn to generate ERDs equivalent in strength to those generated by healthy individuals.

The effects on the analysis results of multiple comparisons should be discussed. Each set of features (ERD/S strengths and PLV values) was divided into four time segments and four frequency bands across two conditions. Therefore, 32 comparisons were made for each of the features (ERD/S values and PLVs). It should be noted, however, that many of the observed significant differences between the groups occurred in stable regions. For example, the majority of the significant differences in ERD/S strength occur in the time segments 4–6 and 6–8 s. Additionally, the investigated frequency bands are known to be involved with motor processes. We therefore suggest that application of a Bonferroni correction for multiple comparisons would be inappropriate here, as it takes no account of these regions of significant differences.

The findings that there are significant effects of age (upper beta) on the ability to separate ERD strength are of some interest. However, these effects are not reliably repeated across frequency bands, time segments, or conditions. The lack of repeatability suggests that these effects may be falsely positive, arising from the multiple comparisons made in the analysis.

The differing numbers of trials between participants and groups was hypothesized to be a significant factor. However, this was not observed to be the case. Additionally, it is important to note that it is common in BCI studies to attempt to determine motor control intention from a relatively small number of trials. Thus, the small number of trials used here represents a realistic challenge, while the larger number of participants adds robustness to the results.

Our findings may be contrasted with those in Pires et al. (2011), in which no differences were observed in P300-BCI performance when comparing between healthy users and users with CP. However, it is important to note that differences in profiles of P300 ERPs compared to SMR activity make comparison between these studies non-trivial. Furthermore, only three individuals with CP participated in the work described in Pires et al. (2011) and these were not differentiated from users with amyotrophic lateral sclerosis (ALS).

In contrast, Nam et al. (2012) compared functional integration, measured by coherence, during a P300 BCI control task performed by individuals with CP, ALS, and healthy controls. A lower BCI accuracy and information transfer rate was found for individuals in both the motor disabled groups (Nam et al., 2012). This was seen to occur alongside an increase in localized coherence during the task in healthy participants when compared to participants in the groups of motor impaired individuals. The difference between electrophysiological activity during MI when compared to P300 means a direct interpretation of these results against MI is not possible. However, they do indicate that some difference in performance at a BCI task may be observed in individuals with CP and that this may also relate to changing levels of connectivity.

Of particular note is that our work examines ERD (based upon the Fourier transform) and phases (based upon non-linear analysis) separately, as these have been shown to exhibit different time courses (Sweeney-Reed and Nasuto, 2009). Previous studies have investigated connectivity in the brain, during BCI control tasks, via the coherence measure (e.g., Krusienski et al., 2012). Coherence is a measure of amplitude and phase. By separating them, we have been able to reveal different aspects of neural processing and increase our understanding of the underlying physiology.

These findings have potential implications for research into the use of BCIs by individuals with CP. First, smaller ERD strengths are harder to differentiate reliably from on-going EEG activity. Hence, MI-BCI control accuracy may be expected to be lower for individuals with CP. Second, BCIs for neurofeedback rehabilitation efforts could, for example, be tailored to encourage greater ERD strength. On the one hand, a case study has already demonstrated improvement in ERD-based classification rates following

neurofeedback (Neuper et al., 2003). On the other hand, we postulate that such neurofeedback may, additionally, increase the ability of this user group to accurately control their own motor functions.

Additionally, the lower ERD strength exhibited in individuals with lesions occurring in early childhood compared to lesions occurring in adulthood (e.g., stroke) suggests that delivering neurofeedback rehabilitation in childhood to individuals with CP may be one promising route of enquiry. This may encourage early neuro-plastic changes and allow acquisition of motor control, which would otherwise prove more challenging.

There are some limitations to our study: The heterogeneity of our CP participants means that we do not have enough participants to provide statistical evidence that the variation in the specific diagnoses of the participants with CP would explain the high variability of ERD/S strengths in that group. Another possible limitation was that the age of the participants was not matched. We did, however, find that this factor did not have a significant effect in our regression analysis.

In future work we intend to explore differences between individuals with CP and how this relates to their ability to produce ERD/S responses and control a BCI. We will also attempt to use the knowledge gained from this study to expedite the development of BCIs that work as effectively as possible for individuals with CP.

CONCLUSION

A significant difference was found between individuals with CP and healthy individuals in terms of the strength of the ERD response, PLV strength, and phase dynamics measured from them during hand and feet MI tasks. Individuals with CP produced significantly lower ERD strengths and PLVs. This suggests that efforts to develop MI-BCIs for individuals with CP must be tailored to the lower ERD response and differences in connectivity strengths expected in this population. Therefore, providing reliable BCI control to users with CP presents a greater challenge than providing BCIs to healthy users.

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