Multimodal Brain-Computer Interface Intervention for Upper Extremity Motor Function Rehabilitation Poststroke

By

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Dedication

For my family, my parents, their parents, and Richard E. Lund.

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It is both right, and just to acknowledge the stroke survivors who voluntarily contributed their time and effort to generate the data that I was fortunate to use in the preparation of this document. I would also like to acknowledge their families and caretakers who helped make their participation possible and from whom I learned that it is easier to stand when others stand beside you.

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Dissertation Abstract

Introduction: Each year, nearly 800,000 people in the United States experience a new or recurrent stroke. Stroke is a leading cause of acquired long-term disability that current standard of care treatments fail to adequately address. Multimodal BCI-FES intervention can leverage neuroplasticity to drive physical capacity improvements for survivors.

Methods: Stroke survivors, 18 years of age or older, completed up to 15 hours of closed-loop, multimodal BCI-FES intervention where FES of the stroke-impaired hand was contingent on intent-to-move brain signals recorded by scalp EEG over sensorimotor cortices.

Results: 64% (9/14) showed some positive change in ARAT at completion and approximately 43% (6/14) of the participants had changes of minimal detectable change (MDC = 3 pts) or minimally clinical important difference (MCID = 5.7 points) with more BCI runs correlating with greater physical improvements by completion. BCI-FES intervention induced significant increase in Mu rhythm desynchronization and increased functional connectivity of ipsilesional motor areas, toward the ipsilesional motor (BA 4) and ipsilesional premotor cortices, and these brain signal changes were related to adaptive changes in objective and subjective measures of behavior.

Conclusion: Multimodal BCI-FES of the stroke impaired extremity contingent on participant-generated EEG scalp recorded motor command signals elicits subsequent signaling in multiple native sensory and motor circuits that enhance and refine experience-dependent neuroplasticity in the sensorimotor system driving neurophysiological changes that promote functional recovery of the stroke-impaired upper extremity.

Chapter 1
INTRODUCTION

Stroke is most often caused by a reduction or interruption of blood supply to parts of the brain resulting in sustained damage, which may produce a variety of symptoms including weakness or paralysis of an extremity. Not all survivors receiving physical therapies fully recover disrupted motor functions, and many continue to experience physical impairment long after traditional windows of care close. Each year, ~795,000 people experience a new or recurrent stroke in the United States (Virani et al., 2021). Potential recovery from stroke follows an important initial timeline with recovery potential decreasing as time passes since the initial stroke insult. Spontaneous recovery may occur; however, natural recovery and recovery potential plateau six to twelve months after insult, leaving more than half of stroke survivors with some level of lasting hemiparesis or hemiplegia requiring a lifetime need for care, making stroke a leading cause of serious long-term acquired disability in the United States (Virani et al., 2021).

Stroke-related economic burden is immense and increasing at a rapid rate. In 2014-2015, the direct and indirect cost of stroke in the United States was estimated to total $45.5 billion (Virani et al., 2021). The estimated direct cost of stroke was $28 billion and indirect cost (lost future productivity) $17.5 billion (Virani et al., 2021). Between 2015 and 2035, total direct medical stroke-related costs are projected to increase significantly, to $94.3 billion, with much of the projected increase in costs arising from those >80 years of age (Virani et al., 2020). Stroke-related costs, therefore, are disproportionally associated with long-term care and rehabilitation. Paradoxically, long-term stroke rehabilitation is disproportionately difficult to obtain as most healthcare payers cover only a limited number of rehabilitation visits during traditional care windows, leaving an unmet need for affordable care options beyond the standard clinical care window for patients living with acquired motor disabilities. To meet this increasing public health challenge, it is imperative to develop novel therapeutic approaches that offer stroke survivors more cost-effective and efficacious treatment options that improve their quality of life.

Traditional and Alternative Therapy Options in Stroke Rehabilitation

Conventional stroke rehabilitation approaches are interdisciplinary in nature. Dominated by physical therapy (PT), often provided in combination with occupational and speech therapies, and constraint-induced movement therapy (CIMT) (Fleet et al., 2014) (Kwakkel et al., 2015), the main aim of traditional therapeutic approaches is recovery of speech and improved functional use of impaired extremities in an effort to facilitate activities of daily living (ADLs) and foster survivors' functional independence, thereby enhancing quality of life. Strong evidence exists that rehabilitation approaches that promote intense, highly repetitive active functional use of the impaired limb result in the largest therapeutic benefits (Pollock et al., 2014) (Veerbeek et al., 2014). Gains in movement capability that result from physical exercise, however, are mostly task-specific and restricted to the trained functions and activities. Moreover, participation in active movement training and CIMT requires sufficient residual motor capabilities, which precludes participation of severely impaired individuals, especially during the time-critical, early phases poststroke.

Clinical interest in new therapeutic approaches in which physical exercise is combined with innovative, BCI-based treatments that may induce and/or facilitate experience-dependent brain plasticity, such as transcranial direct current stimulation (tDCS) (Lindenberg et al., 2010b) (Lindenberg et al., 2010a), transcranial magnetic stimulation (TMS) (Smith and Stinear, 2016), robot-aided therapy (Babaiasl et al., 2016) (Baniqued et al., 2021), virtual reality (VR) (Laver et al., 2015) (Johnson et al., 2018), and other BCI-mediated interventions is growing rapidly (for recent BCI reviews, please see (Bockbrader et al., 2018) (Bai et al., 2020) (Simon et al., 2021). BCI-mediated interventions offer the unique potential to rehabilitate motor dysfunction following brain injury, such as stroke, regardless of level of impairment or time since the injury occurred. For example, some stroke survivors retain the capability to attempt movements with their impaired extremity during all phases poststroke and, therefore, it may be prudent to guide BCI-mediated rehabilitation toward adaptive neuroplastic changes associated with BCI-induced restoration of functional capacities rather than improved physical abilities. Importantly, BCI-based treatments allow rehabilitation of stroke survivors to commence during crucial (early) time windows

poststroke and would provide alternatives for more severely impaired individuals or those who have not yet regained any overt movement capacity and, therefore, are not able to benefit from traditional physical therapy.

Despite recommendations from the 2009 workshop sponsored by the NIH Blueprint for Neuroscience Research that heralded the translation of neuroplasticity as key to developing guidelines for innovative, effective clinical therapies in rehabilitation (Cramer et al., 2011), widespread adoption of BCI-mediated therapeutic approaches in clinical settings has not (yet) been realized, in part because of insufficient evidence supporting their effectiveness, and in part because of practical, technological, and logistical factors, including high equipment costs, limited portability of equipment and the need for extensive expert supervision (Baniqued et al., 2021) (Simon et al., 2021). In order for more widespread use clinically, BCI-mediated interventions must not only provide high quality rehabilitation, but they must also be evidence-based, cost-effective, user-friendly, and they must be able to actively engage both patients and caregivers while, ultimately, be adaptable for home use (Remsik et al., 2016) (Simon et al., 2021).

Neuroplasticity and Stroke Rehabilitation

Stroke allows the opportunity to study the neuroplastic recovery processes that are believed to be responsible for the re-establishment of motor capacity and function following disruption to or destruction of the functionally connected networks in the adult human brain, such as the motor network. Studies have documented changes in brain activity at various stages of stroke and the plasticity mechanisms observed in the post-stroke period are understood to be distinct from the neuroplastic, or learning processes, observed in an intact, healthy brain (Zeiler and Krakauer, 2013). Mechanisms of neuroplasticity during the post-stroke recovery period, either through spontaneous recovery or through traditional rehabilitative approaches (Saur and Hartwigsen, 2012) (Cramer et al., 2000) (Ward et al., 2003a) were once thought to be time-limited (Zeiler and Krakauer, 2013); however, recent studies suggest that additional recovery may

still be possible for many stroke survivors through either alternate mechanisms that emerge during rehabilitation or through simple persistent practice.

Studies of poststroke recovery suggest that unlocking latent recovery potential results from training of beneficial patterns of neural reorganization poststroke. Spontaneous or traditionally facilitated recovery of language function after stroke provided evidence to characterize these changes in the context of a three-phase model in which an initial reduction in brain activity is followed by a compensatory increase in activation among similar brain areas and, finally, a restoration to normal-like activation during a task (Saur et al., 2006). Other studies suggest recovery is partially dependent on lesion location and size with patients suffering from smaller strokes relying more heavily on perilesional recruitment and patients with larger strokes relying on recruitment of the analogous contralesional brain areas, those of the other hemisphere (Schlaug et al., 2011).

While the resulting use of the non-lesioned hemisphere is viewed as compensatory and beneficial, some researchers have suggested that contralesional recruitment, at the expense of increased ipsilesional recruitment and activation of the surviving native brain areas, may represent inefficient or maladaptive changes, and that these improperly molded adaptations may underly the traditional recovery plateau characteristic of the chronic stage of stroke recovery. There is evidence that the normalization of task-related activation and functional connectivity strength between nodes of relevant attention networks correlates with functional recovery over time, supporting the distributed injury hypothesis in which functional deficits arise from impairments or imbalances of activity among one or more nodes of a task-relevant network independent of whether such nodes overlap with the area of physical injury (Corbetta et al., 2005) (He et al., 2007a) (Mazrooyisebdani et al., 2018). An examination of resting state functional connectivity patterns in stroke patients with neglect also found disruptions in functional connectivity among areas of the dorsal and ventral attention networks to correlate with impaired performance on attention-based tasks in the acute stage of stroke recovery (He et al., 2007b).

Longitudinal studies of poststroke functional recovery of the motor system have demonstrated similar increases in the activity of brain regions anatomically isolated from the stroke region shortly after the stroke event, with contralesional hemisphere over-activity typically returning to normal physiological levels after six to twelve months in well-recovered survivors (Loubinoux et al., 2003) (Ward et al., 2003a) (Rehme et al., 2011b) (Rehme and Grefkes, 2013). This decrease in task-related activation in the contralesional hemisphere has been further correlated with functional recovery of ipsilesional brain areas and with behavioral outcomes independent of stroke severity or recovery rate (Ward et al., 2003a) (Young et al., 2014a) (Young et al., 2015) (Young et al., 2016) (Biasiucci et al., 2018). Studies of stroke survivors who experience spontaneous recovery, or recovery facilitated through traditional rehabilitation methods, have demonstrated that after an initial period of compensatory over-activation of analogous contralesional brain regions, task-related brain activity that returns to a normal-like pattern or lateralization of activation tends to be associated with better recovery of motor ability in chronic stroke patients (Turton et al., 1996) (Cicinelli et al., 1997) (Traversa et al., 1997) (Marshall et al., 2000) (Calautti et al., 2001) (Johansen-Berg et al., 2002) (Richards et al., 2008) (Dimyan and Cohen, 2011). One 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), but also support the idea that stroke recovery depends, at least in part, on the functional coordination and activation of the contralesional hemisphere (Kopp et al., 1999) (Lotze et al., 2006) (Carter et al., 2010a; Carter et al., 2010b) (Richards et al., 2008). Optimal patterns of functional brain reorganization from the study of one therapy modality, however, may not be generalizable to other therapy modalities, such as BCI designs. For example, two studies following similar populations of chronic stroke patients found motor function gains to be associated with increased ipsilesional activation or with increased contralesional recruitment during motor tasks of the affected hand after using BCI and gesture therapy, respectively (Ramos-Murguialday et al., 2013).

The brain activation or reorganization patterns found to correlate with improved outcomes using newer approaches, such as BCI therapy, may also depend on stroke location, regardless of whether training with a BCI device is used to modulate activity in lesioned or nonlesioned cortices, and the degree of corticospinal tract damage that resulted from the stroke event (Young et al., 2014c) (Young et al., 2016) (Song et al., 2014a; Song et al., 2015b) (Newton et al., 2006) (Jayaram and Stinear, 2008). It may not be necessary, however, to identify an optimal pattern of change common across therapy modalities if a given approach is able to induce neuroplastic change and, thereby, maximize functional recovery in stroke patients. Understanding these patterns of neuroplastic change might then serve simply to allow for optimization within the application of a particular modality. More research into the relative contributions of inter- and intra-hemispheric task-specific brain activity and changes are needed to better understand the adaptive and maladaptive nature of such changes in stroke survivors and their relative contributions to motor recovery in these individuals.

Multimodal Sensory Feedback (Visual, FES, Tongue Stimulation) in Stroke Rehabilitation

Visual and Virtual Reality

The use of virtual reality environments, either in place of or as a supplement to traditional therapy, to facilitate motor recovery after stroke has been shown to be effective (Turolla et al., 2013) (Thielbar et al., 2014). Virtual reality environments allow for a variety of rehabilitative strategies to be encouraged and practiced, including motor imagery, attempted (i.e., actual) movements, and attempted movements coordinated with sensorimotor feedback. Visual feedback and gaming elements have been incorporated in various BCI systems for motor rehabilitation after stroke (Buch et al., 2008) (Daly et al., 2009) (Prasad et al., 2010) (Shindo et al., 2011) (Takahashi et al., 2012) (Mukaino et al., 2014) (Ono et al., 2014). In such systems, visual information is often presented on a display screen to cue participants and/or provide real-time feedback of neuromodulatory attempts. Gaming elements can be used to further motivate and reward successful task-specific neural activity. As new technologies are developed that make the incorporation of on-screen visual feedback, gaming elements, and virtual reality (VR) in stroke rehabilitation more accessible, it may be possible to further improve user motivation and engagement in

rehabilitation tasks, which may drive the production of more functionally relevant or purposeful movements during therapy (Rand et al., 2014) (Stinear, 2016) (Stinear et al., 2017a; Stinear et al., 2017b), leading to greater clinical fidelity and efficacy beyond the intervention setting (Saposnik et al., 2014).

Functional Electrical Stimulation in Stroke Rehabilitation

Functional Electrical Stimulation (FES) has been used as a traditional motor intervention in stroke survivors with persistent motor deficits and evidence supports the efficacy of FES as an adjuvant to traditional therapies particularly when administered within the first 6 months of stroke (Miller et al., 2010) (Bai et al., 2020) (Simon et al., 2021). FES involves using non-invasive electrical current delivered by electrodes on the skin (e.g., of the forearm) to facilitate movement of a stroke-impaired or paretic muscle. FES is employed by some stroke survivors to stimulate a lower extremity to improve walking (Taylor et al., 2013) and is sometimes applied to a paretic upper extremity (UE) to improve motor function of an arm or hand (Hughes et al., 2014). FES-facilitated improvements in motor function after stroke have been attributed to a recovered ability to voluntarily contract impaired muscles, reduced spasticity, and improved muscle tone of the stimulated muscles, which can also result in increased range of motion of joints in the impaired limb (Kawashima et al., 2013). It is not well understood to what degree various neural mechanisms may drive these changes. One model suggests that proprioceptive sensory input, along with visual perception of the movement and the resulting perception-action coupling may promote adaptive neural reorganization and motor learning in a Hebbian-like neuroplastic fashion (Wang, 2007). However, standard rehabilitative therapies using FES are a largely passive process with minimal coordination between the FES and the mental tasks required of the stroke survivor. Traditionally, FES is administered independently of concurrent brain activity and the lack of contingent activity may limit the efficacy or translatability of standard FES therapies (Biasiucci et al., 2018).

FES may be combined with BCI technology to create a facilitated muscle activation contingent on user-generated neural activity (Biasiucci et al., 2018) (Young et al., 2014d). Such a closed-loop design may leverage mechanisms of neuroplasticity to drive volitional, functional recovery of impaired muscles.

In such a design, the FES acts as feedback for the user to guide or reward targeted neuromodulation and contingent activation of impaired musculature. The use of FES as a feedback modality for a BCI device (i.e., a BCI-FES device) ideally activates the FES only when appropriate brain signals are detected during the user's attempts to move, synchronizing facilitated motion with modulated brain activity (Biasiucci et al., 2018) (Simon et al., 2021). This approach builds on the neural reorganization thought to be induced by FES alone and makes it contingent on the active neuromodulatory and neuroplastic motor learning aspects inherent in the standard BCI paradigm (i.e., closed-loop design). When BCI and FES are combined, they facilitate the traditional forward model of motor control by providing a contingent consequence of ongoing movement attempts, which the brain uses to close the feedback loop of the inverse model creating an environment conducive to motor learning. Such facilitated closed-loop conditioning may further strengthen the central-peripheral connections necessary for the recovery of motor function after stroke, making BCI-FES intervention potentially more efficient, and more effective than either use of BCI, or FES individually.

Biasiucci and colleagues have demonstrated the efficacy of a paired BCI-FES device and offered explanations of potential neural mechanisms behind the resulting neuroplasticity and behavioral changes evidenced in their study (Biasiucci et al., 2018). EMG-triggered FES designs have also demonstrated intent-to-move contingent FES stimulation has therapeutic efficacy (Shindo et al., 2011). Emerging evidence from our group and others suggest that BCI-FES devices, when combined with physiotherapy techniques (Prasad et al., 2010) (Ramos-Murguialday et al., 2013), assist stroke survivors to recover motor function (Takahashi et al., 2012) (Mukaino et al., 2014; Ono et al., 2014) (Young et al., 2015) effectively through FES facilitated muscle stimulation paired with movement related brain signals (Simon et al., 2021).

Tongue Stimulation (Cranial Nerve non-invasive neuromodulation)

Non-invasive cranial nerve neuromodulation, or tongue stimulation (TS), involves the application of small electrical impulses to the dorsal surface of the tongue. Delivered using a surface array of

electrodes placed on the tongue and held in place by pressure from the tongue against the roof of the mouth, the electrical stimulation acts as a sensory supplementation tool (e.g., when a BCI device is used by a blind person or person with hemifield visual neglect), or to facilitate neural recruitment (Kaczmarek et al., 1991) (Wildenberg et al., 2010) (Kaczmarek, 2011) (Wilson et al., 2012).

As a means of sensory substitution, evidence suggests that TS can be used as a means of communicating visual (Chebat et al., 2007) and vestibular (Tyler et al., 2003) (Danilov et al., 2007) (Badke et al., 2011) information to individuals with deficits in these modalities. Further, evidence of reduced nystagmus (i.e., uncontrollable eye movements) in blind individuals using this type of sensory substitution have also suggested a link between non-visual sensory input and ocular motor activity (Nau et al., 2012).

Some TS approaches deliver electrical impulses to the tongue not to provide information related to any external state or stimulus or facilitate sensory transduction and translation but, instead, to reduce sway in balance-impaired individuals (Wildenberg et al., 2010) (Wildenberg et al.). In this way, TS is also being studied as a means of improving balance and gait in patients with spinal cord injury (Chisholm et al., 2014). In these designs, electrical impulses are typically pulsed at a set frequency. Mechanisms underlying such improvements may involve engagement of the balance-processing network in the pons (Wildenberg et al., 2011). Connectivity analyses have also proposed models in which information-free TS initially interfaces with the central nervous system at the brain stem with stimulation then propagating further to the cortex through supramodal information transfer (Wildenberg et al., 2013). TS can be successfully incorporated into a BCI system as a form of sensory substitution sufficient to allow both blind and sighted individuals to control a two-dimensional cursor in a target attainment task by modulating stimuli on the tongue to match the targets and movements being presented visually on screen (Kaczmarek, 2011) (Wilson et al., 2012).

While serving as a potential means of sensory substitution for users unable to follow visual cues and feedback typically presented during BCI therapy, the incorporation of this type of TS may also act as

an additional form of feedback for sighted individuals concurrently tracking on-screen cues. A secondary benefit to incorporating TS during BCI intervention is the potential for promoting sustained beneficial neuromodulation in the motor system like that observed during gait and balance studies mentioned previously.

Brain-Computer Interface with Functional Electrical Stimulation Applications in Stroke Rehabilitation

Closed-loop, EEG-based BCIs employ multimodal sensory feedback to provide the user with a noninvasive neural interface that can be used to teach functionally relevant and therapeutically viable command signals for applications in poststroke upper extremity motor rehabilitation or to substitute or augment residual neuromuscular outputs. In these devices, user-generated unique and measurable modulations in sensorimotor rhythms (SMRs) (i.e., event-related synchronization, ERS) and/or event-related desynchronization, ERD), extracted from EEG activity associated with movement intent during voluntary real, attempted, and/or imagined movements are translated into external command signals which, in turn, are used to control movement of a virtual cursor on a screen (Wolpaw et al., 1991) (McFarland et al., 2000) (Schalk et al., 2004) (Schalk et al., 2008) (Schalk, 2009) (Schalk and Mellinger, 2010) (Nam et al., 2011) (Wilson et al., 2012) and functional electrical stimulation of specifically targeted muscles or muscle synergies (De Marchis et al., 2016), contingent on user generated motor command signals (Biasiucci et al., 2018). Furthermore, by monitoring multimodal sensory feedback (e.g., vision of a cursor on the screen, somatosensory feedback associated with FES-induced movements, electrotactile tongue stimulation, etc.), BCI users are enabled to learn through consequence how to adjust modulations in their SMRs to improve, and fine-tune command signals.

Recent meta-analyses and reviews have highlighted the efficacy of EEG-based BCI use in stroke rehabilitation (Soekadar et al., 2014) (Cervera et al., 2018) (Bai et al., 2020) (Simon et al., 2021). Moreover, BCI paradigms utilizing FES and/or attempted voluntary movements of the impaired extremity are most effective in the rehabilitation of upper extremity (UE) motor function poststroke because they

induce and/or facilitate adaptive neuroplastic changes which reorganize functional neural activity, thereby directly linking movement intent with muscle contraction (Ackerley et al., 2007) (Ackerley et al., 2014) (Jang et al., 2016) (Biasiucci et al., 2018) (Cervera et al., 2018) (Nishimoto et al., 2018) (Remsik et al., 2018) (Tabernig et al., 2018) (Bai et al., 2020) (McCabe et al., 2015; Pundik et al., 2015) (Bai et al., 2020) (Simon et al., 2021).

Closed-loop, EEG-based BCI-FES systems combined with standard physical rehabilitation approaches have been validated and proven efficacious in the rehabilitation of upper extremity motor function poststroke (ClinicalTrials.gov study ID NCT02098265) (Young et al., 2014a; Young et al., 2014c) (Young et al., 2015) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). A multimodal BCI-FES system elicits positive changes in the primary outcome measure (ARAT score: Arm Reach Action Test) (Lyle, 1981) as well as beneficial physiological changes in secondary outcome measures of neural activity (e.g., Mu ERD) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). The system's efficacy relies on 1) EEG acquisition and signal processing to extract real-time volitional and task-dependent neural command signals from cerebral cortical motor areas, 2) FES of muscles of the impaired hand contingent on the motor cortical neural command signals, and 3) multimodal sensory feedback associated with performance of the behavioral task, including visual information, linked activation of somatosensory afferents through intact sensorimotor circuits, and electro-tactile stimulation of the tongue (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). Importantly, BCI-based treatments allow rehabilitation of stroke survivors to commence during crucial (early) time windows poststroke as well as long after stroke insult, and they also provide an alternative treatment option for severely impaired individuals who are no longer able to benefit from traditional physical therapies or have exhausted traditional care windows.

SUMMARY

The application of BCI technology in combination with visual feedback, FES, and TS feedback modalities (i.e., a BCI-FES-TS device) presents the potential to leverage the neuromodulatory and

neuroplastic advantages of these approaches toward functional gains in stroke survivors. An understanding of the underlying neuroplastic processes that mediate functional improvements attained using these devices is critical in further understanding the recovering brain. Insights gleaned from studies using these types of BCI systems for stroke rehabilitation may inform the design of future BCI devices as well. This research is intended to establish the brain and behavioral effects of rehabilitative intervention using a BCI-FES-TS device in stroke survivors with persistent upper extremity motor impairment and to investigate how differences in intervention administration and participant characteristics modify these effects.

While evidence continues to be published supporting the use and research of BCI-mediated recovery in poststroke rehabilitation, factors underlying mechanism(s) of action and efficacy of this technology remain, as of yet, inadequately addressed. For example, the neural mechanism underlying changes observed in stroke survivors using a multimodal BCI-FES intervention, the interplay of inter- and intra-hemispheric brain signal changes, and how they relate to behavioral changes in motor capacity, are yet to be adequately understood or researched. There exists a similar dearth of evidence and understanding of the processes of functional reorganization and recovery in the poststroke brain. This dissertation seeks to address these issues and others to help drive advancement in poststroke motor rehabilitation for the purpose of improving the quality of life for stroke survivors and furthering the understanding of human motor function and recovery through the following three aims.

Specific Aims

Aim 1: Establish clinical efficacy of multimodal BCI-FES for upper extremity motor rehabilitation in stroke survivors.

- Test the hypothesis that multimodal BCI-FES intervention is an effective treatment for stroke survivors with persistent upper-extremity loss.
    - Quantify behavioral changes in primary and secondary outcome measures of stroke survivors receiving BCI intervention compared to a control group.
    - Establish the effects of participant characteristics and BCI intervention parameters on gains in brain and behavioral measures.

Aim 2: Characterize brain-behavioral relationships in recovering stroke survivors receiving BCI intervention.

- Test the hypothesis that multimodal BCI-FES driven motor recovery causes task-related changes in motor network function.
    - Quantify event related desynchronization (ERD) changes in ipsilesional motor network in stroke survivors receiving BCI intervention.
    - Quantify the relationship between motor network brain-signal changes and behavioral changes in the stroke impaired upper extremity following BCI intervention.

Aim 3: Characterize patterns and localization of neuroplastic changes in stroke survivors following BCI intervention.

- Test the hypothesis that changes in motor network functional connectivity correlate with gains in behavioral measures in stroke survivors following BCI intervention
    - Characterize changes in task-related motor network functional connectivity associated with BCI intervention
    - Quantify changes in motor network functional connectivity associated with behavioral gains following BCI intervention.

Chapter 2

BCI-FES with Multimodal Feedback for Motor Recovery Poststroke: Equipment, Materials, and Methods

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ABSTRACT

An increasing number of research teams are investigating the efficacy of brain-computer interface (BCI)-mediated interventions for promoting motor recovery following stroke. A growing body of evidence suggests that of the various BCI designs, most effective are those that deliver functional electrical stimulation (FES) of upper extremity muscles contingent on movement intent. More specifically, BCI-FES interventions utilize algorithms that isolate motor signals -- user-generated intent-

to-move neural activity recorded from cerebral cortical motor areas -- to drive electrical stimulation of individual muscles or muscle synergies. BCI-FES interventions aim to recover sensorimotor function of an impaired extremity by facilitating and/or inducing long-term motor learning-related neuroplastic changes in appropriate control circuitry. We developed a noninvasive, electroencephalogram based BCI-FES system that delivers closed-loop neural activity-triggered electrical stimulation of targeted distal muscles while providing the user with multimodal sensory feedback. This BCI-FES system consists of three components: 1) EEG acquisition and signal processing to extract real-time volitional and task-dependent neural command signals from cerebral cortical motor areas, 2) FES of muscles of the impaired hand contingent on the motor cortical neural command signals, and 3) multimodal sensory feedback associated with performance of the behavioral task, including visual information, linked activation of somatosensory afferents through intact sensorimotor circuits, and electro-tactile stimulation of the tongue. In this report, we describe device parameters and intervention protocols of our BCI-FES system which, combined with standard physical rehabilitation approaches, has proven efficacious in treating upper extremity motor impairment in stroke survivors, regardless of level of impairment and chronicity

INTRODUCTION

Stroke is most often caused by a reduction or interruption of blood supply to parts of the brain resulting in sustained damage, which may produce a variety of symptoms including weakness or paralysis of an extremity. Each year, ~795,000 people experience a new or recurrent stroke in the United States (Tsao et al., 2022). Approximately 610,000 of these are first attacks, and 185,000 are recurrent attacks, making stroke a leading cause of serious long-term acquired disability in the United States (Virani et al., 2021). Potential recovery from stroke follows an important initial timeline as recovery potential decreases the more time passes since the initial stroke. Spontaneous recovery may occur; however, natural recovery and recovery potential plateau, leaving some stroke survivors with a lifetime need for care.

Stroke-related economic burden is immense and increasing at a rapid rate. In 2014-2015, the direct and indirect cost of stroke in the United States totaled $45.5 billion (Benjamin et al., 2019). The

estimated direct cost of stroke was $28 billion and indirect cost (lost future productivity) $17.5 billion (Benjamin et al., 2019). Between 2015 and 2035, total direct medical stroke-related costs are projected to increase significantly, to $94.3 billion, with much of the projected increase in costs arising from those >80 years of age (Virani et al., 2020). Stroke-related costs, therefore, are disproportionally associated with long-term care and rehabilitation. Paradoxically, long-term stroke rehabilitation is disproportionately difficult to obtain as most healthcare payers cover only a limited number of rehabilitation visits, leaving an unmet need for affordable care options beyond the standard clinical care window for patients living with acquired motor disabilities. Therefore, an urgent need exists to reduce cost of care, improve efficacy of existing poststroke rehabilitative therapies, and develop novel therapeutic approaches so as to offer stroke survivors more cost-effective and better treatment outcomes and increased functional independence.

Conventional stroke rehabilitation approaches are interdisciplinary in nature. Dominated by physical therapy (PT), often provided in combination with occupational and speech therapies, and constraint-induced movement therapy (CIMT) (Fleet et al., 2014) (Kwakkel et al., 2015), the main aim of traditional therapeutic approaches is recovery of speech and improved functional use of impaired extremities in an effort to facilitate activities of daily living (ADLs) and foster survivors' functional independence, thereby enhancing quality of life. Strong evidence exists that rehabilitation approaches that promote intense, highly repetitive active functional use of the impaired limb result in the largest therapeutic benefits (Pollock et al., 2014) (Veerbeek et al., 2014). Gains in movement capability that result from physical exercise, however, are mostly task-specific and restricted to the trained functions and activities. Moreover, participation in active movement training and CIMT requires sufficient residual motor capabilities, which precludes participation of severely impaired individuals, especially during the time-critical, early phases poststroke.

Clinical interest in new therapeutic approaches in which physical exercise is combined with innovative, BCI-based treatments that may induce and/or facilitate experience-dependent brain plasticity,

such as transcranial direct current stimulation (tDCS) (Lindenberg et al.), transcranial magnetic stimulation (TMS) (Smith and Stinear, 2016), robot-aided therapy (Babaiasl et al., 2016) (Baniqued et al., 2021), virtual reality (VR) (Laver et al., 2015) (Johnson et al., 2018), and other BCI-mediated interventions is growing rapidly (for recent reviews, please see (Bockbrader et al., 2018) (Bai et al., 2020) (Simon et al., 2021). BCI-mediated interventions offer the unique potential to rehabilitate motor dysfunction following brain injury, such as stroke, regardless of level of impairment or time since the injury occurred. For example, some stroke survivors retain the capability to attempt movements with their impaired extremity during all phases poststroke and, therefore, it may be prudent to guide BCI-mediated rehabilitation toward adaptive neuroplastic changes associated with BCI-induced restoration of functional capacities rather than improved physical abilities. Importantly, BCI-based treatments allow rehabilitation of stroke survivors to commence during crucial (early) time windows poststroke and would provide alternatives for more severely impaired individuals or those who have not yet regained any overt movement capacity and, therefore, are not able to benefit from traditional physical therapy.

Despite recommendations from the 2009 workshop sponsored by the NIH Blueprint for Neuroscience Research that heralded the translation of neuroplasticity as key to developing guidelines for innovative, effective clinical therapies in rehabilitation (Cramer et al., 2011), widespread adoption of BCI-mediated therapeutic approaches clinically has not (yet) been realized, in part because of insufficient evidence supporting their effectiveness, and in part because of practical, technological, and mechanistic factors, including high equipment costs, limited portability of equipment and the need for extensive expert supervision (Baniqued et al., 2021) (Simon et al., 2021). In order for more widespread use clinically, BCI-mediated interventions must not only provide high quality rehabilitation, but they must also be evidence-based, cost-effective, user-friendly, and they must be able to actively engage both patients and caregivers while, ultimately, be adaptable for home use (Remsik et al., 2016) (Simon et al., 2021).

With regard to the above list of requirements for wide-spread adoption of BCI-mediated therapeutic approaches, recent meta-analyses and reviews have highlighted EEG-based BCIs as most

promising in the rehabilitation of stroke survivors (Cervera et al., 2018) (Bai et al., 2020) (Simon et al., 2021). Moreover, BCI paradigms utilizing FES and/or attempted voluntary movements of the impaired extremity are most effective in the rehabilitation of UE motor function poststroke (Ackerley et al., 2007) (Ackerley et al.) (Ramos-Murguialday et al., 2013) (Ackerley et al., 2014) (Jang et al., 2016) (Biasiucci et al., 2018) (Cervera et al., 2018) (Nishimoto et al., 2018) (Tabernig et al., 2018) because they may induce and/or facilitate neuroplastic changes that directly link movement intent with muscle contraction (Pundik et al., 2015) (Bai et al., 2020) (Simon et al., 2021).

Closed-loop, EEG-based BCIs employ multimodal sensory feedback in order to provide a noninvasive neural interface that is used therapeutically to substitute or augment native neuromuscular outputs by translating user-controlled neural activity into functionally relevant and therapeutically viable command signals. More specifically, user-generated unique and measurable modulations in sensorimotor rhythms (SMRs) (i.e., event-related synchronization, ERS) and/or event-related desynchronization, ERD), extracted from EEG activity associated with movement intent during voluntary real, attempted, and/or imagined movements (Wilson et al., 2009a) (Nam et al., 2011) are translated into external command signals which, in turn, are used to control movement of a virtual cursor (e.g., ball) on a screen (Wolpaw et al., 1991) (Schalk et al., 2004) (Schalk et al., 2008) (Wilson et al., 2009b) or functional electrical stimulation of specifically targeted muscles or muscle synergies (De Marchis et al., 2016). Furthermore, by monitoring multimodal sensory feedback (e.g., vision of the ball on the screen, somatosensory feedback associated with FES-induced movements, etc.), BCI users are able to learn through consequence how to adjust modulations in their SMRs to improve and fine-tune command signals.

This chapter includes a presentation of device parameters and intervention protocols of our closed-loop, EEG-based BCI-FES system which, combined with standard physical rehabilitation approaches, has been validated and proven efficacious in the rehabilitation of upper extremity motor function poststroke in our ongoing cross-over controlled clinical trial (ClinicalTrials.gov study ID NCT02098265) (Young et al., 2014c) (Young et al., 2015) (Remsik et al., 2018) (Remsik et al., 2019)

(Remsik et al., 2021). This BCI-FES system elicits positive changes in the primary outcome measure (ARAT score: Arm Reach Action Test) (Lyle, 1981) as well as beneficial physiological changes in secondary outcome measures of neural activity (e.g., Mu ERD) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). The system's efficacy relies on specific targeting of neuromuscular activity contingent on intent-to-move neural signals, recorded with scalp electrodes overlying cerebral cortical sensorimotor areas, as well as concurrent delivery of multimodal sensory feedback through implementation of a chain of straightforward operating procedures described in this report. The scalp EEG signals provide an efficient and practical way to extract, in real-time, the relevant control features, and to deliver the desired feedback to the patients as part of an interactive and closed-loop neural activity-triggered application. We also present supplementary intervention data from three stroke survivors for the purpose of illustrating the utility of this BCI-FES design in rehabilitation at various levels of impairment and chronicity. The present BCI-FES protocol, integrated with standard rehabilitation approaches, may provide a substantial improvement toward sensorimotor functional recovery of the impaired extremity in stroke survivors (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021).

MATERIALS AND EQUIPMENT

The Multimodal BCI-FES

A conventional EEG-based BCI system presents the user with a visual display that represents modulation in SMRs related to movement intent (Pfurtscheller and Berghold, 1989) (Wolpaw et al., 1991) (Pfurtscheller and Lopes da Silva, 1999) (Leuthardt et al., 2004) (Schalk et al., 2004) (Pfurtscheller et al., 2005a) (Daly and Wolpaw, 2008) (Young et al., 2014c). The BCI-FES system design presented here extends this standard paradigm by presenting the user with a virtual environment in which goal-directed motor learning is reinforced explicitly. The BCI-FES design also allows for FES-induced upper extremity movement facilitation contingent on the cerebral cortical motor signals associated with movement intent, and for multimodal sensory feedback (e.g., visual, electro-tactile, and somatosensory).

EEG Cap Configuration & Signal Acquisition

EEG electrodes are positioned on the scalp according to the standard 10-20 system, grounded to Fpz, and referenced to an electrode placed on the back of the participant's right ear. Signals from the C3, C4, and Cz electrodes, overlying the sensorimotor cortices, are recorded in every session and are used to drive horizontal cursor movement (Schalk et al., 2004) (Schalk et al., 2008) (Wilson et al., 2009a). EEG activity is recorded from sixteen locations with sintered Ag/AgCl active electrodes using a sensor cap attached to a 16-channel bipolar recording system (g.LADYbird-g.GAMMAcap, Guger Technologies, Graz, Austria). Electrode signals are amplified (g.USBamp, Guger Technologies, Graz, Austria) and digitized by sixteen independent 24-bit A/D converters at 38.4 kHz per channel. EEG activity is sampled at 256 Hz, using a 0.1-100 Hz band-pass filter, and a 58-62 Hz notch filter.

Signal Processing

Signal acquisition, online signal processing, and behavioral task (cursor movement and virtual targets) are controlled using custom software developed on the BCI2000 platform (Schalk et al., 2004). Following basic filtering, the signal enters into a spectral estimator which computes a continually updated estimate of the spectrum of its input data. For each updated computation, the module uses a 0.5 s window of past data and applies an autoregressive (AR) algorithm to estimate spectral amplitude. The AR algorithm computes an autoregressive model of its input data using the maximum entropy method (Marple Jr and Carey, 1989) and outputs an estimated power spectrum collected into bins. Bins are of 2 Hz width each with the center of the first bin being 0 Hz and the center of the last bin being 40 Hz. This results in 21 bins, with the first bin covering the DC range -1 to +1 Hz (which due to symmetry of the transfer function is twice the integral from 0 to 1 Hz) and the last bin covering 39 to 41 Hz.

Results of the spectral estimator are used in a linear classifier through a process of feature extraction and translation. The linear classifier computes a projection of a high-dimensional signal feature into a low-dimensional classification space. In our implementation, spectrum amplitudes from C3, and C4 at both 8 Hz and 18 Hz, are translated into the one dimension of the classification space. The classifier output enters a normalization transformation of the form output = (input - o)g, in which “o” is the

normalizer offset value, and "g" is the normalizer gain. Adjusting the offsets for bias of cursor movement in the right or left direction, and gain, controls the speed at which the cursor moves. In essence, the classifier output undergoes a normalization transformation, and is then used as a control signal that specifies one-dimensional horizontal cursor movement in the user application module (Wilson et al., 2009a).

User Application (Visual Presentation)

Following normalization, the control signal is passed to the user application. Throughout the BCI design the user-generated modulation in SMRs is time-locked to the FES and/or output of the tongue-display unit (TDU) (Kaczmarek, 2011) (Wilson et al., 2012) and the visual display presentation. Recognition of attempted right-hand and left-hand movements results in concordant horizontal cursor movement in right and left directions, respectively (Wilson et al., 2009a). Cursor and TDU parameters may be updated once per block of data acquisition. Data is acquired at 256 Hz, and 12 samples compose a single block. This means that the user application is updated at a frequency of 21.3 Hz or every 46.8 ms.

Functional Electrical Stimulation (FES)

FES of the upper extremity (Popovic et al., 2002c) (Popovic et al., 2002a; Popovic et al., 2002b) (Popovic et al., 2004a; Popovic et al., 2004b) (Peckham and Knutson, 2005) (Ragnarsson, 2008) (Page et al., 2009) (Takahashi et al., 2012) (Howlett et al., 2015) (McCabe et al., 2015) (Vafadar et al., 2015) (De Marchis et al., 2016) (Jang et al., 2016) (Kim et al., 2016) (Biasiucci et al., 2018) (Tabernig et al., 2018) (Annetta et al., 2019) (Wilson et al., 2019), an established means for treating neuromuscular treatment following central nervous system (CNS) injury, is delivered in this design through a pair of square electrodes up to 2" x 2" in size, placed securely on the affected forearm using highly conductive electrolyte spray. Stimuli are produced by a LG-7500 Digital muscle Stimulator (LGMedSupply, Cherry Hill, NJ, USA). Commercially available stimulus isolation units ensure clean, opto-electrical isolation. The FES electrodes are placed superficial to the flexor digitorum superficialis muscle in order to facilitate repeated whole hand grasping (i.e., hand and finger flexion) or superficial to extensor digitorum communis in order to facilitate repeated whole hand opening (i.e., hand and finger extension), according

to participant preference at individual BCI sessions. FES is computer controlled using an Arduino Uno R3 microcontroller board (Adafruit Industries, New York, NY, USA) and a simple reed relay circuit. FES amplitude is set to elicit observable muscle contractions (e.g., whole hand grasping or extension) without pain to the user. The pulse rate of the stimulation is 60 Hz, in order to produce tetanic contraction of the muscles, and the pulse width is 150 μs. Stimulation intensity is initially set to zero and is adjusted in steps of 0.5 mA, unless the stimulation becomes uncomfortable for the participant. In the event of discomfort, the stimulation intensity is returned to the nearest previous level not producing discomfort. The device is never set to deliver an output >50 mA.

Tongue-Display Unit (TDU)

The TDU, illustrated in Figure 2 at the end of this chapter, has been described in detail previously (Kaczmarek, 2011) (Wilson et al., 2012). The TDU is battery-operated and generates patterned, low-voltage stimulation to a 12×12 electrode array that is positioned on the anterior dorsal portion of the participant's tongue (Kaczmarek, 2011) (Wilson et al., 2012). Similar to the FES, the TDU intensity is set, prior to any trials, to the highest level of intensity not producing discomfort in the participant. The TDU electrode grid supplements the visual cursor and target task; it aids participants with potential visual field impairments (Bach-y-Rita, 2004). When the target appears on either the left or right side of the display screen, the TDU electrode array is activated concurrently and concordantly. The stimulation persists on the side of the tongue according to target location until the user successfully drives the virtual cursor into the target area. In the event of a successful attempt (i.e., cursor enters target area), the entire electrode array is activated until the trial times out. In the event of an unsuccessful attempt, in which the user is unable to drive the cursor into the target area before the trial time expires, the TDU ceases to deliver stimulation to the side of the tongue corresponding to the side of the screen where the target was presented.

Stimulation intensity may be adjusted after each run to ensure that the subject is able to perceive the stimulation and correctly interpret the target presentation without discomfort. All stimuli are presented

within the participant's preferred stimulus intensity range, from sensation threshold to below maximum level, without discomfort. In case the stimulus-evoked sensation becomes aversive, stimulus intensity is reduced, or the stimulus array is removed from the subject's mouth entirely. No data are available on the effects of long-term electro-tactile stimulation of the tongue; however, the study group has neither observed, nor reported any tissue irritation following tongue stimulation from over 200 subjects tested over a 10-year period (conducted under previous UW-Madison HS-IRB Protocols 2000-0119, 2000-0527, 2001-364, 2004-375, 2005-0187, 2005-0192, and 2007-0251).

Multimodal BCI-FES Intervention

Task schedule

The BCI tasks consists of an open-loop (Li et al., 2014) task and two closed-loop tasks (i.e., BCI with visual feedback only, and BCI with visual feedback & electro-tactile stimulation). The general difference between the open- and closed-loop tasks is the absence or presence, respectively, of SMR-driven feedback to the participant in the form of movement of a virtual cursor on the display screen toward a target or goal area (Schalk et al., 2008) (Wilson et al., 2009a) and associated electro-tactile sensory feedback. Such feedback is understood to aid participants in learning to control SMR modulation and successfully perform the task. As no feedback is given during the open-loop task, no learning is expected to occur during that condition. The open-loop task is designed as an initial assessment to establish, and train, the optimal SMR features that the participant will use to control the behavior of the SMR-driven feedback (i.e., the cursor/ball) during the closed-loop tasks.

Familiarization with the BCI Device and Procedures

The first BCI session aims to introduce the participant to the BCI device and protocol. During this initial session, the EEG cap, FES device, and TDU device are administered as described above. Stroke survivors may present with a myriad of cognitive, affective, and physical impairments (Tsao et al., 2022) and out of respect for individual participants' needs and abilities, the researchers may allow a few runs of each BCI task condition for the purpose of introducing participants to the task requirements and feedback sensations. During these preliminary sessions, the study protocol will be faithfully administered as

described. Subsequent runs in all sessions aim for all BCI task conditions to be performed consistent with protocol demands.

Participant Criteria

Participants are individuals with motor impairments due to stroke, regardless of stroke severity, stroke chronicity (i.e., time since injury), or gender. The effectiveness of the present BCI intervention in the rehabilitation of motor impairments poststroke has been validated as part of on-going clinical trial NCT02098265, in which stroke survivors participated in 9-15 BCI intervention sessions (2-3 sessions per week) lasting up to 2 hours, for a maximum of 30 hours of intervention. Participants also contributed to behavioral testing prior to the first BCI session (i.e., Pre), at the midpoint of intervention (i.e., Mid), immediately following the last intervention session (i.e., Post), and at a one-month, post-intervention follow-up (i.e., Follow-up).

METHODS

Setup

The EEG cap must be positioned on the user's scalp such that the electrode locations correspond with those specified by the 10-20 international system. All 16 electrodes used must record electrophysiological signals with optimal signal-to-noise ratios (Wilson et al., 2009a).

Protocol

Open-loop Screening Task

A session begins with an open-loop hand movement assessment task, in which no performance feedback is given. The first two trials of the pre-intervention screening phase incorporate "actual, attempted" hand movements (Ackerley et al., 2011) (Ackerley et al., 2014) in response to written cues displayed on the computer screen, and corresponding verbal instructions (i.e., Left, Right, Rest), illustrated in Figure 1 at the end of this chapter. The last two runs of the pre-intervention screening phase incorporate "imagined" hand movements in response to the same written cues and corresponding verbal instructions. To accommodate initial movement capacity and the nature of each participant's motor impairment, participants are instructed to execute hand movements according to their individual treatment goals and physical capabilities but are instructed to execute repeated hand grasping motions in either hand

when cued. Each screening EEG data file contains 15 trials of rest, left hand and right-hand movements (i.e., 5 trials for each of the three conditions), separated by an interstimulus interval of 1.5-2 s. The order of trials in a run is random. Each of the trials has a duration of four seconds. Coefficients of determination (r-squared) are calculated in order to evaluate the spectral difference at each frequency bin between the attempted left- and right-hand movement conditions. Finally, control features are selected as the left and right channel-frequency pairs (i.e., C3-Cz & C4-Cz electrodes as shown in for both the Mu (8-12 Hz) and Beta (18-26 Hz) frequency bands.

EEG Calibration

Data recorded during the initial screening task may be analyzed using BCI2000's Offline Analysis MATLAB-based tool in order to determine the optimal SMR features for online control of the subsequent closed-loop tasks (Schalk et al., 2004) (Wilson et al., 2009a) (Schalk and Mellinger, 2010). The channels and frequency bands chosen should be consistent with known properties of cortical SMRs associated with attempted hand movements (i.e., locations and frequencies consistent with the contralateral cerebral cortical motor areas and the corresponding electrodes (e.g., C3, C4), and centered near the Mu (8-12 Hz), and Beta (18-26 Hz) frequency bands (Pfurtscheller and Berghold, 1989) (Wolpaw et al., 1991) (Pfurtscheller et al., 1997) (Pfurtscheller, 1999) (Pfurtscheller, 1999; Pfurtscheller and Lopes da Silva, 1999) (McFarland et al., 2000) (Neuper and Pfurtscheller, 2001) (Wolpaw et al., 2002) (Schalk et al., 2004) (Neuper et al., 2005) (Neuper et al., 2006) (Daly and Wolpaw, 2008) (Schalk et al., 2008) (Ackerley et al., 2011) (Ackerley et al., 2014). Control features may be standardized across subjects (i.e., 8 Hz and 22 Hz) or optimized for each individual participant at each session. This procedure is designed to determine the features that optimize subject-specific signals that are used to drive the cursor movement and deliver concurrent FES to the stroke impaired musculature. Although selected control features may differ between participants, the common underlying principles are that the features selected are overlying sensorimotor cortices, and that they are in the expected physiological range of motor output (i.e., ~6-30 Hz) so as to ensure they represent user-driven motor signals associated with movement intent.

Closed-loop Cursor & Target Task

The control features are translated into feedback (i.e., ball/cursor movement) of the subsequent BCI tasks as described by Schalk and Mellinger (Schalk et al., 2004) (Schalk and Mellinger, 2010). An autoregressive spectral analysis (Marple Jr and Carey, 1989) first estimates the spectral power of the control features. The resulting control feature signals are then put into a classification algorithm that performs a linear transformation of these signals, which are translated into the feedback behavior of the cursor on the screen, the FES adjuvant, and the TDU stimulation. The prevailing logic is that the strongest SMR features (within the prespecified Mu (8-12 Hz) and Beta (18-26 Hz) frequency bands (Pfurtscheller and Berghold, 1989) (Wolpaw et al., 1991) (Pfurtscheller et al., 1997) (Pfurtscheller and Lopes da Silva, 1999) (Pfurtscheller and Lopes da Silva, 1999) (McFarland et al., 2000) (Neuper and Pfurtscheller, 2001) (Neuper et al., 2006) (Ackerley et al., 2011) (Babiloni et al., 2016) of attempted movement define the control features used for each participant in the subsequent closed-loop (i.e., Cursor Task) condition (Wilson et al., 2009a).

Visual Feedback Only

The first ten runs of the closed-loop BCI task condition present the user with visual feedback of their modulated sensorimotor rhythm features through a virtual ball-and-target game (i.e., closed-loop Cursor Task). During this task, users perform the same type of repeated attempted hand movements as in the screening task described in Open-loop Screening Task section. Participants learn to control the movement of the virtual ball (i.e., cursor) displayed on the computer screen by modulating their SMR activity as they perform the task. The SMR activity, related to attempted left (or right) hand movements, are translated into leftward (or rightward) ball movement. At the start of each trial, the participant is instructed to look at the center of the blank screen. Two seconds later, a virtual target appears randomly on the left or right side of the screen. After the target is displayed for two seconds, the cursor (ball) appears in the center of the screen and the participant is instructed to move the ball towards the target by eliciting SMR modulation using attempted repeated hand movements, as described in 3.2.1. For a trial to be considered successful, the ball must hit the target within 2.5-5 seconds of its appearance. If the attempt

is successful, the target appears to illuminate and maintains this "reward" presentation for 0.5 seconds, as illustrated in Figure 2 at the end of this chapter. If the trial is unsuccessful after the maximum time allowed (five seconds), the cursor and target disappear within the subsequent 0.5 s interval. Immediately following task completion (hit or miss), an intertrial interval of four seconds commences and the presentation sequence is repeated. Each run consists of 10 trials.

Adjuvant Stimulus Administration

Following 10 completed runs (i.e., 100 trials) with visual feedback only, FES (functional electrical stimulation) and TDU (tongue-display unit) (Kaczmarek, 2011) (Wilson et al., 2012) are incorporated. Driven by the modulation in SMRs generated by engagement with the virtual ball-and-target task, FES is applied to the targeted muscles of the impaired hand and electro-tactile feedback is presented through the TDU. In this way, participants can incorporate visual, electro-tactile, and proprioceptive feedback, when possible, associated with muscle activation for the purpose of modulation and monitoring of volitional movements. The ensemble of multimodal feedback serves as adjuvant stimulus to engage paretic musculature and somato-motor circuitry in improved, more natural execution of the motor plan (e.g., attempted voluntary hand flexion) and to provide enhanced multimodal performance feedback to the user. The modulation of SMR activity needed to perform the task well directly links movement intent to the facilitated muscle contraction. Rewarding this linkage via the cursor-and-target task is hypothesized to facilitate motor learning and potential recovery (Bach-y-Rita, 1981) (Bach-y-Rita) (Nudo and Milliken, 1996; Nudo et al., 1996a; Nudo et al., 1996b) (Nudo and Friel, 1999) (Friel and Nudo, 1998) (Nudo et al., 2001) (Kleim et al., 2002) (Schaechter et al., 2002) (Rossini and Dal Forno, 2004b; a) (Plautz and Nudo, 2005) (Strangman et al., 2005) (Cramer and Riley, 2008) (Jayaram and Stinear, 2008) (Murphy and Corbett, 2009) (Popovic et al., 2009) (Wang et al., 2010) (Ackerley et al., 2011) (Cramer et al., 2011) (Dimyan and Cohen, 2011) (Pekna et al., 2012) (Takeuchi and Izumi, 2012b; a) (Wolpaw, 2012) (Jiang et al., 2013) (Soekadar et al., 2014; 2015) (Volz et al., 2014) (Nudo, 2015) (Reinkensmeyer et al., 2016) (Biasiucci et al., 2018) (Mohanty et al., 2018). BCI-driven FES is only applied to muscles of the impaired limb and is delivered only and concurrently with cursor

movement toward the targeted side in order to ensure that muscle stimulation never occurs while participants attempt to move the ball toward their unimpaired side.

Functional Electrical Stimulation

Following ten complete runs of BCI (visual only feedback), BCI+FES trials are initiated. FES settings are adjusted at a safe and effective intensity level as described above. The appropriate muscle(s) for targeted stimulation are identified and electrodes are attached accordingly. The aim is to elicit motor responses in the impaired hand that reflect whole hand flexion or extension. If some fingers are moving more than others, the electrodes are repositioned until fingers open/close evenly when stimulated manually. With help of the participant, the appropriate level of stimulation is established that is both comfortable for the participant and produces recognizable grasping movement of the impaired hand as described in Open-loop Screening Task section.

Tongue Display Unit (TDU)

Following ten complete BCI+FES runs, BCI+FES+TDU runs are initiated.

Open-Loop Exit Screening Task

Sessions end with a repetition of the open-loop screening task, described previously.

Minimizing Risks

Subjects are under supervision at all times during the experiments and are easily able to communicate discomfort or a need for respite. The preferred stimulus intensity range for FES is determined by beginning with low amplitude stimulation and gradually increasing the amplitude until the participant demonstrates a motor response or indicates that their maximal comfort level has been reached, as described previously. The amplitude threshold for eliciting a motor response generally occurs well below the amplitude threshold for stimulation discomfort. The preferred range of tongue stimulation intensity is similarly specified, but rather than looking for a motor response, the maximal range is that which provides a clear sensory percept without producing discomfort in the participant. Stimulus intensity range is determined by beginning with low amplitude stimulation and gradually increasing the amplitude until the participant indicates their maximal comfort amplitude has been reached, as described

previously. It is imperative that one listens to and engages with the participant to meet their needs and maintain honorable adherence to essential principles of care such as respect for individual persons, beneficence, and justice.

RESULTS

Clinical efficacy of the present BCI-FES intervention in the rehabilitation of motor impairments poststroke has been validated as part of on-going clinical trial NCT02098265, in which stroke survivors participated in 9-15 BCI intervention sessions lasting up to two hours, for a maximum of 30 hours of intervention per participant (Young et al., 2014a; Young et al., 2014c) (Young et al., 2015) (Remsik et al., 2018). We have published evidence demonstrating improvements in both objective and subjective measures of behavioral outcomes used to assess stroke-related motor impairments (Remsik et al., 2018) (Remsik et al., 2019). For example, we have reported moderate improvements in Action Research Arm Test/Fugl-Meyer scores (Remsik et al., 2018) as compared to a control group and significantly increased grip strength (Remsik et al., 2019). Moreover, we have presented neurophysiological evidence that our BCI-FES design is able to generate significant and adaptive changes in EEG activity and brain connectivity (Mazrooyisebdani et al., 2018) (Mohanty et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). Specifically, increases in task-related ipsilesional Mu (8-12 Hz) ERD, were significantly correlated with improvements in measurements of motor recovery (Remsik et al., 2019) and functional connectivity (Remsik et al., 2021).

Table 1 summarizes a sample of validated outcome measures designed to test and quantify different functional domains that may be affected by stroke or brain injury resulting in motor loss and may be affected by this BCI-FES device design. The list is not exhaustive. In addition to behavioral and task performance measures specific to a given rehabilitation target, such as grip strength, foot-drop, spasticity, or otherwise. It is important researchers and clinicians consider assessments of outcome measures in other domains because of the rich functional interconnectedness of the sensorimotor cortex with the rest of the brain (Simon et al., 2021).

Objective and subjective measures of motor capacity and function, measures of task and brain activity, and activities of daily living (ADLs) (e.g., Barthel Index, Motor Activity Log, etc.) are important metrics to consider when assessing the impact of BCI-FES on users (Simon et al., 2021) (please see Supplementary Materials Table 1).

DISCUSSION

BCI-FES systems 1) have the potential to be significantly more cost-effective than traditional rehabilitations (i.e., naturally modifiable and can be configured to address individuals' needs or environmental constraints such as budget, space or location), 2) provide therapy that supplements, and potentially shortens or replaces conventional poststroke care, and 3) provides rehabilitative therapy that may be superior to present day standards of care, particularly in both the most severely impaired and chronic survivors of stroke. Primary outcome scores (e.g. Action Research Arm Test, Fugl-Meyer Test) following intervention suggest that the present BCI-FES design is able to deliver moderate improvements in UE motor function supported by evidence of similar improvements in several other subjective and objective measures of stroke impact (Song et al., 2014c) (Young et al., 2014c) (Song et al., 2015a) (Young et al., 2015) (Young et al., 2016).

The present non-invasive, EEG-based BCI-FES intervention has the potential to improve rehabilitation poststroke over and above the conventional standards of care in use at the present time. Each of the three example participants included herein demonstrated an increased capacity to perform the BCI-FES task accurately over the course of intervention. Although it may take time for a user to become proficient at the BCI-FES task requirements (i.e., volitional control of the cursor's movement across the screen), nearly all users who are able to understand the instructions are able to use and benefit from the technology. While the features of rehabilitation might differ from person to person, the mechanisms of motor learning and brain-computer interfacing are ubiquitous as they rely on native CNS functioning. The BCI-FES concept is generalized across participants in that the means for using a BCI naturally exist in most all participants, yet the application of the intervention may be personalized. Thus, the BCI-FES

intervention presented here allows for clinical translation of BCI-FES technology in a manner that tailors the therapy to the needs and circumstances of specific individuals, thereby providing a basis for personalized, precision medicine.

Recovery of motor function poststroke follows specific neurological patterns and is so far limited in capacity by, among other factors, the individual participant's presenting functional abilities. None the less, BCI devices can be used by participants regardless of severity of stroke lesion or motor impairment and offer a novel tool for delivering treatment options to those who are unable to participate in or benefit from more traditional means of motor rehabilitation. Further, the BCI intervention design presents a means to investigate and improve participant motor performance, beyond the capacity of conventional methods and expectations of care. The portability, adaptability (i.e., gamification) and efficacy of our BCI-FES design are ideally suited to extend windows of care for chronic severely impaired stroke survivors by providing continued care options beyond traditional clinical settings into, for example, the participant's own home.

The potential therapeutic benefits of using closed-loop neural activity-triggered feedback systems (i.e., BCI-FES) for motor rehabilitation are being investigated in stroke survivors (Feng and Belagaje, 2013). Either FES, which targets specific muscle sets via myotic stimulation, or robotic assistance, which acts to replace control of the impaired limb, are able to produce movement of the paretic limb. BCI-FES designs can be configured to drive volitional upper extremity movement rehabilitation and may be tailored to precisely modulate the strength and timing of muscle activity of the recovering motor system (Cho et al., 2011) (Stinear, 2016). Recent evidence suggest that BCI-FES is an effective means of delivering treatment beyond traditional clinical windows and BCI-FES designs may be more effective than other existing BCI designs (Biasiucci et al., 2018) (Simon et al., 2021). The optimal inclusion of adjuvants and the physical design of a BCI system for stroke motor rehabilitation are yet undefined in the field. Evidence suggests that BCI-FES systems, in combination with physical therapy (e.g., goal-directed motor behaviors, functionally relevant movements as compared to imagined movements, etc.), may

facilitate superior improvements in motor recovery by inducing neuroplastic changes in appropriate control circuitry, compared to traditional BCIs, occupational therapies, or robotic rehabilitations (Cervera et al., 2018) (Carvalho et al., 2019) (Simon et al., 2021). Multimodal feedback from visual, somatosensory, and electro-tactile afference, contingent on EEG-signals related to voluntary movement intent, drives sensorimotor integration and may represent a mechanism, motor learning, responsible for BCI-FES induced motor recovery (Biasiucci et al., 2018). To date, of the various configurations of BCI devices in use for motor recovery, BCI-FES designs have demonstrated superior clinical efficacy (Bai et al., 2020) (Simon et al., 2021). In other procedures, FES is used therapeutically to aid voluntary motor function during motor rehabilitation (Merletti et al., 1975) (Popovic et al., 2002a; Popovic et al., 2002b; Popovic et al., 2002c) (Popovic et al., 2004a; Popovic et al., 2004b) (Popovic et al., 2009) (Popovic, 2014) and contingent integration may be important for successful rehabilitation (Iftime-Nielsen et al., 2012). As demonstrated by Biasiucci and colleagues, in their BCI-FES versus sham FES experimental design, the inclusion of the FES adjuvant incorporates somatosensory contributions to the BCI user's goal-directed motor plan that are thought to encode afferent information of consequence to the brain facilitating a closed-feedback loop (Biasiucci et al., 2018).

Specifically, in our BCI-FES design, the facilitation of myotic activation contingent on EEG-recorded intent-to-move neuromodulation may foster multimodal -- cutaneous, proprioceptive, and visual -- afference that aids in enhancing adaptive intra- and interhemispheric network connectivity changes (Remsik et al., 2021). Suitable activation of sensorimotor feedback loops may drive conditioning as well as activity-dependent, Hebbian plasticity (Bach-y-Rita, 1981) (Bergquist et al., 2011) (Wolpaw, 2012). Whereas this study design (NCT02098265) does not allow us to draw the same conclusions as Biasiucci and colleagues with respect to the precise mechanisms or clinical significance of the FES adjuvant, our results and our BCI-FES device are similar to those of Biasiucci and colleagues (Biasiucci et al., 2018) (Remsik et al., 2021). Therefore, it is likely that the clinically relevant functional gains obtained with the BCI-FES system described here are due to similar strict contingency of BCI-driven FES detailed by

Biasiucci and colleagues. However, while Biasiucci and colleagues offer evidence for such a mechanism, the specific sensorimotor substrates and mechanisms that underlie the observed improvements in motor learning remain unknown (Christensen and Grey, 2013).

The present evidence-based protocol delivers meaningful functional improvements; however, additional research is needed to identify the neural circuitry and mechanisms responsible (Biasiucci et al., 2018) (Bai et al., 2020). Future research must be directed towards identification and tracking of the genesis and progression of associated neuroplastic changes, and the relative importance of changes in intra- and interhemispheric network connectivity. Continued research into the mechanistic origins of any such neuroplasticity will help improve rehabilitation strategies in order to enable caregivers to provide maximal benefit to patients (Bai et al., 2020) (Simon et al., 2021).

Limitations

While small-scale, observational findings in the use of BCIs for motor rehabilitation have highlighted the promise of this technology for stroke survivors, a standardized BCI-FES intervention schedule and dosing regimen has yet to be recognized for optimal treatment of hemiparesis (Remsik et al., 2016) (Bai et al., 2020) (Simon et al., 2021). Development of a standard rehabilitation protocol requires large cohort studies and increased monitoring in clinical settings beyond the laboratory.

Heterogeneity in intervention affects may be compounded by the limitations of any given outcome measure (i.e., sensitivity, suitability), and the large variability in location and extent of stroke-induced damage among survivors. As stroke may affect either multiple aspects of one's life, or a stereotyped movement (e.g., hand grasping), it is important to employ a diverse battery of neuropsychological assessments in order to capture any adaptive or maladaptive effects that may result from the intervention (Table 1).

Design

Adjustments to various components of the BCI-FES intervention design (e.g., more intervention, more frequent intervention, etc.), display enrichment (e.g., enhanced gameplay and graphical

presentation), or improvements in functional (i.e., task) relevance (e.g., simple instructed wrist supination and pronation, compared to pouring a virtual glass of liquid into another virtual glass etc.) might further facilitate motor recovery in stroke participants using a BCI-FES with multimodal feedback. Such enhancements to BCI intervention designs might improve participants' engagement, attention, and motivation during the intervention sessions, potentially increasing their neuroplastic affects (Seo et al., 2019). Participants might also benefit from increased monitoring of self-reported fatigue or motivation throughout the intervention sessions. BCI-FES is most effective when participants are actively engaged in the task and, therefore, it may be important to measure changes in engagement due to fatigue, boredom, or other limitations, and lapses in concentration (Seo et al., 2019). Additional research on the effects of these and other considerations not raised here, may help to increase the effectiveness of BCI-FES interventions for upper extremity motor recovery in stroke survivors.

Control Features

Although the specific control features that are selected to trigger FES may vary from participant to participant, the common principle between participants is that the features selected derive from EEG frequency bands and cerebral cortical areas known to be associated with sensorimotor processing and voluntary motor output. Thus, the BCI device is adapted to each participant individually, which aids participants with different motor capacities and brain volumes to use the device (Bundy et al., 2012).

Dose

Data presented in other work from our laboratory (Young et al., 2014a) (Song et al., 2015b) (Young et al., 2015) (Young et al., 2016) (Mazrooyisebdani et al., 2018) (Mohanty et al., 2018) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021) suggest that a dose of two-hour sessions for up to 30 hours with this BCI-FES intervention design is sufficient to positively effect motor recovery in stroke participants. Furthermore, a larger number of runs of this BCI-FES intervention results in greater brain and behavioral changes associated with recovery (Remsik et al., 2018) (Remsik et al., 2019). Further research, specifically investigating how behavioral improvements depend on dosage categories (i.e., low, medium, or high) is needed to optimize dosage for specific individuals.

Supplemental Stimulation Adjuvants

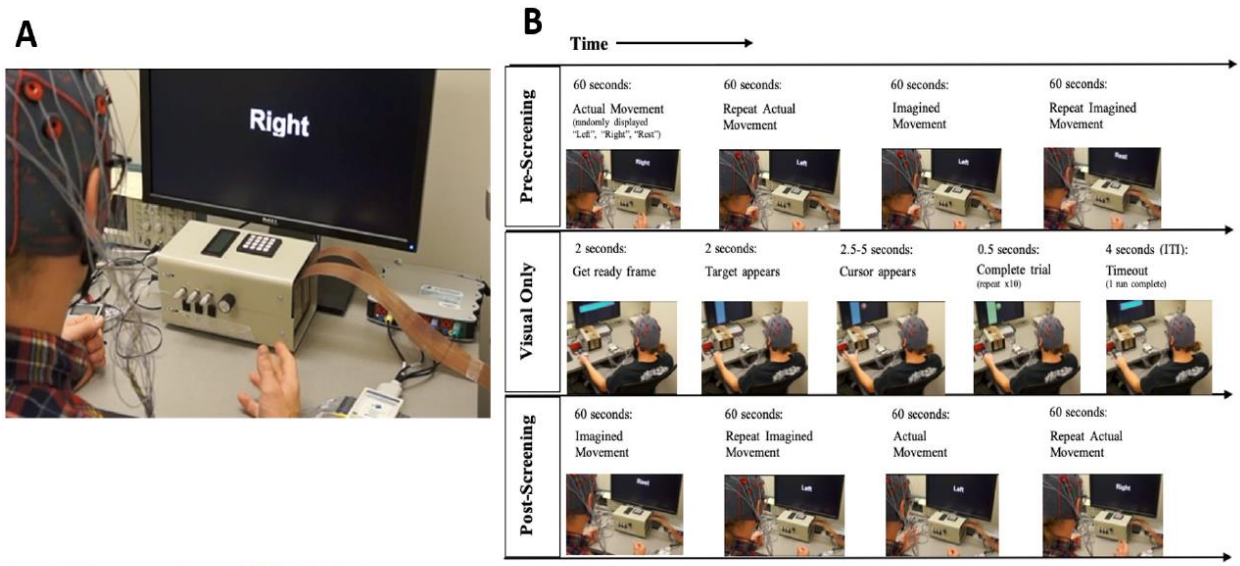
Incorporating an adjuvant stimulus component (e.g., FES, TDU, haptic feedback, etc.) and multimodal feedback into the BCI intervention design may engender a more dynamic rehabilitative approach (Bach-y-Rita, 1990). Clinical fidelity is thought to depend largely on the sensory feedback that establishes the non-invasive closed-loop system (Biasiucci et al., 2018) (Simon et al., 2021). The feedback of the BCI-FES design can help shape the motor efference produced in cerebral cortical motor areas, and when this association remains consistent over time, the brain will adapt. The BCI-FES design presented here can drive that adaptation toward useful recovery of motor function. Inclusion of adjuvants may also pose specific limitations, such as managing consistent placement of the FES electrodes across subjects, across sessions, as well as variations in sensitivity threshold and willingness of participants to receive adjuvants that deliver stimulation. The present BCI-FES design limits participants to simple whole hand flexion or extension of the fingers (i.e., repeated hand grasping) and some stroke survivors may benefit from practicing different or more complex movements, which the current BCI-FES configuration is not designed to support.

CONCLUSION

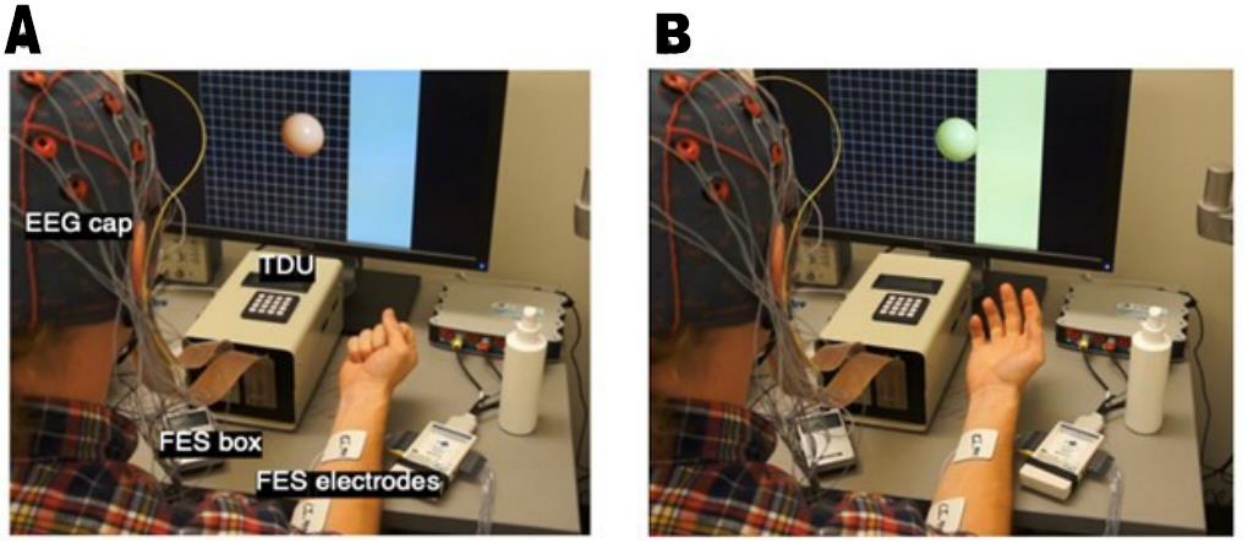
BCI-FES designs are cost-effective and superior means of delivering poststroke care that are capable of supplementing or partially replacing traditional physical therapy regimens. The BCI-FES is a most promising design for the future of BCI-mediated rehabilitation of stroke. Further improvements in BCI design, such as updating to wireless communication between system components, decreasing system size and cost, as well as gamification and simplification of the user interface, will further minimize costly healthcare supervision and, therefore, will increasingly satisfy requirements of healthcare payers for more cost-effective means to supplement and enhance conventional physical therapy for stroke survivors within and beyond traditional care windows.

The multisensory closed-loop BCI-FES intervention design described here has been shown to be safe and effective for stroke survivors at all timepoints after their initial insult. This intervention design effectively enables users to either continue their recovery beyond standard clinical care windows (i.e.,

well after their CNS insult – e.g., chronic stroke) or it can function as a supplement to standard of care therapies available within standard clinical care settings (e.g., acute stroke). The closed-loop nature of this BCI-FES design may enhance experience-dependent neuroplasticity (Bach-y-Rita, 1981) (Bach-y-Rita, 1990) (Nudo, 2003a; c; b) (Wolpaw, 2012), especially in the sensorimotor system, driving neurophysiological changes that promote functional recovery of stroke-impaired UE, regardless of other factors. In this BCI-FES intervention design, FES of the stroke impaired muscles contingent on participant-generated control features in the recorded EEG signals associated with movement intent elicits subsequent signaling in multiple native sensory (cutaneous, proprioceptive, visuo-motor, etc.) and motor circuits that likely enhance and refine subsequent intent-to-move signals (i.e., motor command signals) and efficacy of subsequent motor behavior. This work represents a first step towards clinical translation of a standardized design for BCI-FES interventions.



BCI Setup and Task Block Design
A: Participant set up with BCI interface for open-loop trials. Setup includes monitor, EEG cap, and amplifier.
B: Session and block design: Every session starts with an open-loop condition, followed by the intervention (closed-loop) condition which is followed by a repeat of the open-loop condition.
Open-Loop: Participants are notified that the run will begin. First the cue appears on the screen with corresponding auditory instruction for the open-loop screening condition.
Closed-loop: The target appears on one side of the monitor, followed by the cursor ball in the closed-loop. Once the participant guides the ball into the target, the trial is complete.
Figure 1: Multimodal BCI-FES session sequence and protocol. A) Open-loop task. B) Session protocol steps.



Intervention Setup and Cursor Ball Display
A: Cursor appears in the middle of the screen following target presentation on one side or the other. The target is represented by the blue strip on one side of the monitor. EEG cap, FES box, FES electrodes, and TDU box are labeled to show device setup.
B: Cursor ball moves toward the target as cued by EEG-recorded intent to move brain signals. If the target is not hit in the maximum time allowed (e.g., 2.5-5 s) the trial is aborted. If the user moves the cursor into the target, the trial is a success. There are 10 trials in one run.

Figure 2: Multimodal BCI-FES device arrangement and closed-loop task. A) Device components. B) Closed-loop task.

Primary Outcome Measure	Description
Action Research Arm Test (ARAT) (Lang et al., 2006) (Lyle, 1981)	The ARAT is designed for evaluation of upper extremity function. This test consists of total of 19 items divided into 4 sections for Grasp, Grip, Pinch and Gross Movements. Item in each section is graded on a 4-point ordinal scale (0 cannot perform any part of the test, 3 performs normally). The maximum possible total score is 57.
Secondary Outcome Measures	
Barthel Index (Collin et al., 1988)	The Barthel Index measure a person's daily functioning (activities of daily living and mobility).
Center for Epidemiologic Studies-Depression Scale (CES-D): (Radloff, 1977)	The CES-D is a self-report scale and includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. Responses are recorded using a 4-point Likert scale ranging from rarely (scored 0) to all of the time (scored 3), and points are summed across the 20 items to provide a total CES-D score.
DSST Mesulam & Weintraub Cancellation task for hemispatial neglect (Weintraub, 1985)	The Mesulam–Weintraub Cancellation task consists of four test forms utilizing structured and unstructured arrays of verbal and non-verbal stimuli. Subjects are asked to circle all of the targets they can find using different colored pencils so that after every ten targets or a specified time the participant changes pencils so that their search pattern may be identified. The targets are the letter "A" in the verbal and the symbol "☼" in the non-verbal arrays (~ 10 minutes).

Electromyography (Kauffman et al., 2021)	EMG is the recording of changes in skin voltage caused by contraction of the underlying muscles. This recording (Kauffman et al.) will be obtained using the EMG recording equipment of the BIOPAC systems (http://www.biopac.com/researchApplications.asp?Aid=41&Level=1).
Flanker task (Eriksen and Eriksen, 1974)	Flanker task is an executive function/attention task. Subjects are presented with visual stimuli and asked to respond to the direction of a left or right pointing arrow and ignore flanking arrows that point in the opposite direction as the target arrow.
The Fugl-Meyer (FM) motor assessment (Fugl-Meyer et al., 1975)	The FM motor assessment is used to measure voluntary limb movement. It includes the upper extremity (UE) subscale (33 items; score range, 0–66) and the lower extremity (LE) subscale (17 items; score range, 0–34) for a total motor FM score of 100.1.
Geriatric Depression Scale (Yesavage et al., 1982)	Depression Screening: For subjects 65 and older, we use the Geriatric Depression Scale -15 Item. The GDS or the Mood Assessment Scale screens for depression in the elderly. The GDS taps affective and neuropsychological symptoms of depression and consists of 30 yes/no questions. For subjects younger than 65, we use the Center for Epidemiological Studies -Depression Scale. The CES-D is a self-report scale and includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. The final score spans from 0 to 60, with a higher score indicating greater impairment (~10 minutes).
Hand-grip Strength (Boissy et al., 1999)	Hand grip strength is assessed with a dynamometer. Participants are asked to squeeze as hard as possible and then release. Three trials are performed with the affected and unaffected hand.
Hopkins Verbal Learning Test (HVLT) (Benedict et al., 1998)	The HVLT is a brief test of verbal learning and memory and consists of a list of 12 nouns (targets) with four words drawn from each of three semantic categories (~ 10 minutes).
Mini-Mental Status Examination (MMSE) (Tombaugh and McIntyre, 1992)	The MMSE is a screening tool that provides a brief, objective measure of cognitive function.
Modified Ashworth Scale (Gregson et al., 1999)	MAS assesses spasticity in wrist, elbow, and finger flexion/extension muscles, on a six-point scale (0, no increase in muscle tone to 4, limb rigid in flexion or extension).
Montreal Cognitive Assessment (MOCA) (Toglia et al., 2011)	MOCA to test subjects for cognitive impairments (~10 minutes).
Motor Activity Log (MAL) (Van der Lee et al., 2004)	MAL is a structured interview developed to assess the use of the more affected upper extremity in real-world daily activities. Participants are asked to rate how well (Quality of Movement) and how much (Amount of Use) they use their affected arm to accomplish 14 activities of daily living.
Modified Health Questionnaire	Modified Health Questionnaire to document the general physical health and social habits of all subjects.
The National Institute of Health stroke scale (NIHSS) (Lyden et al., 2009)	The NIHSS is a standardized method to measure the level of impairment caused by a stroke.

Nine-hole peg test (9HPT) (Mathiowetz et al., 1985; Beebe and Lang, 2009b)	The participant sits at a table and is asked to take 9 dowels (9 mm diameter, 32 mm long) from the tabletop and put them into 9 holes (10 mm diameter, 15 mm deep) spaced 50 mm apart on a board. The time to complete this is recorded.
Pain Scale (Wong and Baker, 1988)	Pain Scale: Participants is asked to rate their degree of pain on a scale of 0 (no pain) to 5 (in tears).
Sensory motor computerized task (Chiu et al., 2011)	Sensory motor computerized task: A computerized task testing participants speed and response time is developed in-house. The task requires participants to watch the appearance of a target on the left or right of the screen and to click the target as soon as it appears
The Short-Blessed Test (Katzman et al., 1983)	The Short-Blessed Test, a six-item test, is used as a diagnostic tool to differentiate participants with cognitive impairments from healthy controls. Subjects are asked to answer the items year and month, time of day, count backward 20-1, recite months backwards, and the memory phrase. This test is administered in addition to the MMSE, which also tests for cognitive impairment because the Short-Blessed Test is more sensitive to differences in levels of education and is quicker to administer (~ 3-4 minutes).
Span measures (Tulsky et al., 1997)	Participants recite digit span, forward and backward (measure of working memory)
Stroke Impact Scale (SIS) (Duncan et al., 1999)	The Stroke Impact Scale, or SIS, assesses changes in impairments, activities and participation following a stroke. Scores on the SIS provide an index of clinically "meaningful" change representing the change in the participant's mental and physical abilities concurrent with their performance on the verbal fluency and memory tasks. The 4 physical function domains (strength, hand function, ADL/IADL, and mobility) is collapsed to a physical function subscale. All domain scores range from 0 to 100 with 100 being the best.
Stroop Task (Golden and Freshwater, 1978)	Stroop task is an executive function/conflict resolution task. In this task the participant tries to name the color of the ink in which a word is printed when the word itself is the name of a color other than that of the ink. Typically, one is slower in this situation than if the color word and the name of the color coincide.
Trail Making Tests (Reitan and Wolfson, 1986)	Trail Making Tests provide information on visual search, scanning, speed of processing, mental flexibility, and executive functions.

Table 1: Registry of Relevant Poststroke Outcome Measures

Chapter 3

Behavioral Outcomes Following Brain–Computer Interface Intervention for Upper Extremity Rehabilitation in Stroke: A Randomized Controlled Trial

Remsik AB, Dodd K, Williams L Jr, Thoma J, Jacobson T, Allen JD, Advani H, Mohanty R, McMillan M, Rajan S, Walczak M, Young BM, Nigogosyan Z, Rivera CA, Mazrooyisebdani M, Tellapragada N, Walton LM, Gjini K, van Kan PLE, Kang TJ, Sattin JA, Nair VA, Edwards DF, Williams JC and Prabhakaran V (2018) Behavioral Outcomes Following Brain–Computer Interface Intervention for Upper Extremity Rehabilitation in Stroke: A Randomized Controlled Trial. *Front. Neurosci.* 12:752. doi: 10.3389/fnins.2018.00752

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at:
https://www.frontiersin.org/articles/10.3389/fnins. 2018.00752/full#supplementary-material

Clinical Trial Registration: ClinicalTrials.gov, NCT02098265.

ABSTRACT

Stroke is a leading cause of persistent upper extremity (UE) motor disability in adults. Brain–computer interface (BCI) intervention has demonstrated potential as a motor rehabilitation strategy for stroke survivors. This sub-analysis of ongoing clinical trial (NCT02098265) examines rehabilitative efficacy of this BCI design and seeks to identify stroke participant characteristics associated with behavioral improvement. Stroke participants (n = 21) with UE impairment were assessed using Action Research Arm Test (ARAT) and measures of function. Nine participants completed three assessments during the experimental BCI intervention period and at 1-month follow-up. Twelve other participants first completed three assessments over a parallel time-matched control period and then crossed over into the BCI intervention condition 1-month later. Participants who realized positive change (≥1 point) in total ARAT performance of the stroke affected UE between the first and third assessments of the intervention period were dichotomized as "responders" (<1 = "non-responders") and similarly analyzed. Of the 14 participants with room for ARAT improvement, 64% (9/14) showed some positive change at completion and approximately 43% (6/14) of the participants had changes of minimal detectable change (MDC = 3 pts) or minimally clinical important difference (MCID = 5.7 points). Participants with room for improvement in the primary outcome measure made significant mean gains in ARATtotal score at completion (ARATtotal = 2, p = 0.028) and 1-month follow-up (ARATtotal = 3.4, p = 0.0010), controlling for severity, gender, chronicity, and concordance. Secondary outcome measures, SISmobility, SISadl, SISstrength, and 9HPTaffected, also showed significant improvement over time during intervention. Participants in intervention through follow-up showed a significantly increased improvement rate in SISstrength compared to controls (p = 0.0117), controlling for severity, chronicity, gender, as well as the individual effects of time and intervention type. Participants who best responded to BCI intervention, as evaluated by ARAT score improvement, showed significantly increased outcome values through completion and follow-up for SISmobility (p = 0.0002, p = 0.002) and SISstrength (p = 0.04995, p = 0.0483). These findings may suggest possible secondary outcome measure patterns

indicative of increased improvement resulting from this BCI intervention regimen as well as demonstrating primary efficacy of this BCI design for treatment of UE impairment in stroke survivors.

INTRODUCTION

Stroke

Each year there are approximately 800,000 new incidences of stroke in the United States (Benjamin et al., 2019), and in 2010 there were an estimated 16.9 million stroke events globally (Thom et al., 2006). Stroke occurs as a result of a blockage of blood flow in an area of the brain or by rupture of brain vasculature causing death or damage to local and distal brain tissue. In either etiology, survivors may experience some level of upper extremity (UE) physical impairment. Despite recent advances in acute care, an increasing number of stroke survivors face long-term motor deficits (Benjamin et al., 2019). Costs of care for long-term disability resulting from stroke are substantial with the direct medical costs of stroke estimated to $17.9 billion in 2013 (Benjamin et al., 2019). It is crucial that motor therapy for stroke enhances a survivor's capacity to autonomously participate in activities of daily living (ADLs), thereby decreasing dependency on caregivers as well as the cost and level of care necessary (Dombovy, 2009) (Stinear, 2016). Efficacious motor therapy should be designed to improve the overall quality of life for the individual survivor based on their goals and needs (Remsik et al., 2016) (Stinear).

Need for Treatment

Survivors in the chronic stage of stroke are the most desperate for rehabilitation. Existing pharmacological treatments and behavioral therapy methods primarily serve to treat symptoms associated with stroke (Benjamin et al., 2019) and may not bring about optimal changes in brain function or connectivity (Power et al., 2011). While a growing population of research suggests the greatest potential for recovery in the post-stroke brain occurs within the first months after insult (Stinear and Byblow, 2014; Stinear et al., 2014), neuroplastic capacity has been demonstrated in both acute and chronic phases (Caria et al., 2011) (Ang et al., 2015). Spontaneous biological recovery (SBR) (Beebe and Lang, 2009a; b; Lang et al., 2009) (Nudo and Hillis, 2010) in the initial days and weeks following stroke (acute phase) is thought to represent a critical period in the complex progression of motor recovery, which combines

neurobiological processes and learning-related elements. After this window of SBR, it is posited a sensitive period of neurorecovery persists, plateauing around 6 months post-stroke (Wolf et al., 2006) (Wolf et al., 2010) (Dromerick et al., 2009) (Nudo and Hillis, 2010). Traditional rehabilitation therapies generally lose efficacy after such time and the course of standard of care treatment options is exhausted leaving chronically impaired persons with few options.

Potential for Treatment

Motor and cognitive recovery after these initial windows may no longer occur in the same spontaneous nature as is observed during SBR. However, innovative therapeutic techniques show some efficacy generating functional motor recovery beyond the traditional rehabilitation windows (Nudo and Hillis, 2010) (Ang et al., 2015) (Irimia et al., 2016). Brain–computer interfaces (BCIs), a novel rehabilitation tool, have shown proof of concept for rehabilitating volitional movements in stroke survivors (Muralidharan et al., 2011) (Song et al., 2014c) (Song et al., 2015b) (Young et al., 2014a) (Irimia et al., 2016). In this growing area of research, developing technologies demonstrate promising potential for treating hemiparesis in a clinically viable and efficient manner and they may offer an avenue to increased autonomy for patients reducing their cost and burden of care.

Effectiveness of Current BCI Therapies

There is currently considerable variability in design and efficacy of BCI therapies as well as little consensus with respect to proper arrangement, administration, and dosing (Muralidharan et al., 2011) (Ang et al., 2012; Ang et al., 2013) (Young et al., 2014a) (Ang et al., 2015) (Irimia et al., 2016) (Remsik et al., 2016) (Bundy et al., 2017) (Dodd et al., 2017). Although acute stroke care has improved morbidity outcomes significantly, current treatments for persistent UE motor impairment resulting from stroke offer only limited restoration of UE motor function the further from stroke a survivor progresses (Wolf et al., 2006) (Dromerick et al., 2009) (Benjamin et al., 2019) (Stinear et al., 2017a). Evidence suggests both acute and chronic stroke patients respond to various neuro-rehabilitative BCI therapy strategies and can achieve clinically significant changes in measures of UE impairment (Young et al., 2014a) (Irimia et al., 2016) (Remsik et al., 2016). Furthermore, recent research also suggests that BCI therapy targeted at motor

recovery may provide benefits in other brain regions outside of only the motor network (Mohanty et al., 2018).

Overview of This Study

This post hoc analysis of an ongoing clinical trial (NCT02098265) evaluates the effects of an interventional, non-invasive closed-loop electroencephalography (EEG)-based BCI intervention for the restoration of distal UE motor function in stroke survivors. Participants who showed measurable change in the primary outcome measure were grouped post hoc. This sub-analysis seeks to identify whether there are participant characteristics strongly associated with motor improvement as measured by primary and secondary outcome measures of UE function. These analyses are intended to inform future BCI research approaches and intervention designs as well as suggest and encourage appropriate participant selection.

MATERIALS AND METHODS

Ethics Statement

Participants were recruited as part of an ongoing prospective randomized, cross-over control design stroke rehabilitation study. This study was designed to investigate interventional BCI intervention targeting UE motor function in stroke survivors. This study was approved by the University of Wisconsin Health Sciences Institutional Review Board (Study ID 2015-0469); all subjects provided written informed consent upon enrollment. A CONSORT flow diagram is made available in the Supplementary Material.

Study Design and Subjects

Recruitment and Enrollment

This ongoing study, registered with ClinicalTrials.gov (study ID NCT02098265), utilizes an open call for participants with a wide range of (1) UE hemiparesis resulting from stroke, (2) time-since-stroke, (3) stroke type, (4) lesion location, (5) number of previous strokes, and (6) stroke severity. Subsequent to informed, written consent, stroke survivors were randomized, by permuted-block design accounting specifically for gender, stroke chronicity (< 1 year, ≥ 1 year), and severity of motor impairment (mild, severe) as measured by the Action Research Arm Test (ARAT) (mild = ARATtotal of > 28, severe = ARATtotal ≤ 27) (n = 21, mean age = 61.6 years ± 15 years, 10 female, 4 concordant lesions (stroke lesion impairs preferred dominant hand as assessed by the Edinburgh Inventory [30]), mean chronicity =

1127 days ± 1327 days, 12 participants presented with severe UE motor deficit, mean baseline ARAT score of impaired side = 26.6 ± 26.1, Delayed Therapy Group (DTG) n = 12, Immediate Therapy Group (ITG) n = 9). Chronicity is measured as time since stroke, in days, to baseline measurement day.

Participants	Age Years	Chronicity Days	Severity	Clinical Cause Lesion Location	Baseline ARAT	Completion ARAT	FollowUp ARAT	ARAT Change	FMA-UE Change
1	47-51	160	severe	L-Lateral Medulla	3	2	7	-1 (4**)	-2 (9***)
2	49-53	490	severe	R-MCA Stroke	3	4	8	1* (5**)	2* (11***)
3	76-80	658	mild	Leg/Periventricular White, MHR	57	57	57	0 (0)	0 (0)
4	67-51	2723	severe	R-PLIC Putamen	23	40	39	17*** (16***)	13*** (12***)
5	81-85	580	mild	Cerebellar Vermis	47	52	52	5** (5**)	2* (2*)
6	73-77	197	severe	R-Prefrontal, Midfrontal, Temporal	0	0	3	0 (3**)	0 (7***)
7	62-66	101	mild	R-White Matter	56	57	57	1*(1*)	7*** (7***)
8	40-44	2645	severe	R-Frontal Parietal	7	7	7	0 (0)	0 (0)
9	55-59	588	severe	R-MCA	3	4	0	1* (-3)	2* (-7)
10	45-49	452	severe	L-Hemorrhagic Stroke	0	2	0	2* (0)	4**(0)
11	30-34	494	mild	L-ICA	57	57	57	0 (0)	0 (0)
12	60-64	44	mild	L-PCA	57	57	57	0 (0)	0 (0)
13	57-61	849	mild	L-MCA	57	57	57	0 (0)	0 (0)
14	44-48	3017	severe	R-MCA/ R-FI	3	4	5	1* (2*)	2* (4**)
15	69-73	790	severe	R-MCA/ R-TP	3	0	3	-3 (0)	-7 (0)
16	78-82	631	mild	R-Occipital	57	57	57	0 (0)	0 (0)
17	75-79	5125	severe	R-MCA/ACA	9	11	10	2* (1*)	4** (2*)
18	42-46	177	mild	L-MCA	57	57	57	0 (0)	0 (0)
19	62-66	392	severe	R-Frontal Hematoma	3	5	16	2* (13***)	4* (29***)
20	55-59	2767	mild	R-VAOA, Subarachnoid Hemorrhage	57	57	57	0 (0)	0 (0)
21	69-73	783	severe	R-MCA	0	0	0	0 (0)	0 (0)
Mean	61.6	1127			26.6	28.1	26.8	1.3 (2.2)	1.5 (3.6)
(A) Median	61.9	588			9	11	16	0 (0)	0 (0)
SD	15	1327			26.4	26.3	25.9	3.9 (4.5)	3.8 (7.4)
Mean	61.1	1289			11.4	13.4	14.8	2 (3.4)	2.2 (5.4)
(B) Median	64	584			3	4	7	1 (1.5)	2.0 (3.0)
SD	13.5	1497			18	20.2	19.6	4.7 (5.2)	4.5 (8.5)

ARAT Indicates Action Research Arm Test; FMA-UE Indicates Fugel Meyer assessment of Upper Extremity; MCA Indicates Middle Cerebral Artery; ICA Indicates Internal Carotid Artery; PCA Indicates Posterior Cerebral Artery; FI Indicates Frontoparietal Infarct; TP Indicates Temporalfrontal-Parietal; ACA Indicates Anterior Cerebral Artery; MHR Indicates Motor Hand Region; VAOA Indicates Vertebral Artery Origin Aneurysm; L, Left; R, Right. ARAT Change: Completion- Baseline (FollowUp- Baseline). (A) Indicates descriptive statistics for all ($n = 21$) participants; (B) Indicates descriptive statistics for ($n = 14$) participants able to achieve ARAT improvements (ceilings removed).
FMA-UE is a predicted change that was used to approximate equivalent score that assesses the association between the categorical range of ARAT scores. *Indicates Responder ($\Delta_{ARAT} \geq 1$); ** Indicates Minimal Detectable Change (MDC) ($\Delta_{ARAT} \geq 3$); ***Indicates Minimal Clinically Important Difference (MCID) ($\Delta_{ARAT} \geq 5.7$); .

Participant characteristics are displayed in [Table 1].

Table 1: Participant Demographics and Baseline Characteristics

Inclusion-Exclusion Criteria

Potential participants met inclusion criteria if they were age 18 years or older; had persistent UE motor impairment resulting from stroke; and no other known neurologic, psychiatric, or developmental disabilities. Exclusion criteria were: allergies to electrode gel, surgical tape, and/or metals, concurrent treatment for infectious disease, apparent lesions or inflammation of the oral cavity, pregnancy or intention to become pregnant during the study, and any contraindication for magnetic resonance imaging (MRI). Subjects were excluded from the presented analyses if they (1) failed to complete at least 9 of 15, two-hour BCI intervention sessions occurring at least twice each week, (2) failed to complete all four MRI and behavioral testing sessions occurring in the intervention phase [Figure 1] [see Supplemental Materials, CONSORT Flow diagram].

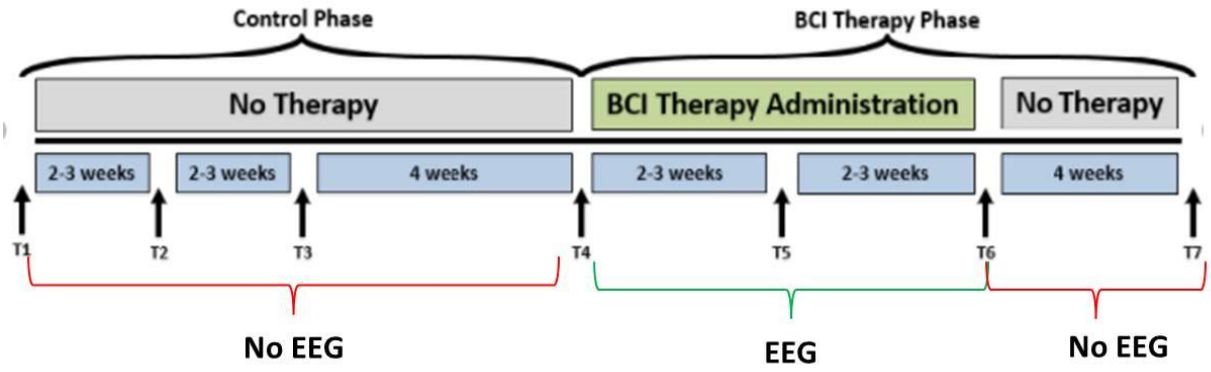


Figure 1: Study design. The time-points at which neuroimaging data were collected are represented by – Tl: Control baseline 1, T2: Control baseline 2, T3: Control baseline 3, T4: Therapy baseline, T5: Mid-therapy, T6: Post-therapy, and T7: One-month post-therapy. While the crossover control group (DTG) completed visits T1 through T7, the immediate therapy group (ITG) group completed visits T4 through T7 only.

Randomization & Study Schema

Participants were randomly assigned to either receive BCI intervention immediately (ITG) following consent or to a delayed therapy group (DTG) wherein participants were neither prohibited continuation of customary care, nor did they receive any BCI intervention. Participants, when receiving

the BCI intervention condition, had at least 9 and up to 15 BCI intervention sessions (two-to-three sessions/week) wherein they received BCI intervention [Figure 3] lasting up to two hours for a potential total dosing of 30 hours of BCI intervention. Along with the BCI intervention sessions, subjects also received fMRI and behavioral testing at four-time points: prior to the first BCI intervention session (baseline, T4), after the first few weeks of intervention (midpoint, T5), immediately following the final intervention session (completion, T6), and again one month after the endpoint assessment (follow-up, T7) [Figure 1]. Later in this publication, the authors will refer to time points 1-4 with the intention of describing time points 1-4 of the intervention phase (T4-7 from Figure 1). Because T1-4 in Figure 1 refer to the control phase, the authors from here forward will refer to any data from these points by explicitly stating when the control phase is being considered.

Crossover Design

Following the final testing session, participants in the DTG cross over to the experimental or intervention phase and begin study visits for the BCI intervention condition as illustrated in Figure 1. For participants in the DTG, the crossover time point (T4) represents baseline as it is measured immediately prior to participation in BCI intervention sessions.

Outcomes

For these analyses, and consistent with original study design, a primary objective outcome measure of UE function, the ARAT (Mathiowetz et al., 1985) (Beebe and Lang, 2009b) (Malhotra et al., 2016), and secondary outcome measures of function (capacity and performance) including the self-report Stroke Impact Scale (SIS) (Duncan et al., 1999) (Lin et al., 2010), Hand Grip Strength (An et al., 1980) (Malhotra et al., 2016), and the 9-Hole Peg Test (9HPT) (Mathiowetz et al., 1985) were assessed in the 21 participants who met the aforementioned criteria. The primary outcome measure, with registered minimal detectable change (MDC) and minimal clinically important difference (MCID) values (ARAT MDC = 3-point change, MCID = 5.7-point change) (Lyle, 1981), was chosen to obtain clinically reliable measures of UE motor function change as a result of BCI intervention. 9HPT was included in this report as an additional objective (time) measure of motor function. The 9HPT is an assessment of fine motor control

and speed of distal UE movement capacity and performance. The 9HPT requires finger dexterity and grip and supplements the ARAT as they both assess gross UE capacity and function. This study analyzes ARAT scores, 9HPT performance by the affected UE (9HPTaffected), and SIS sub-scores of the impaired hand from the four time points, illustrated in Figure 1. The Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) is another objective measure of function commonly used to assess UE capacity in several BCI studies. Although the FMA-UE was not intended as an assessment in this design, associations between categorical ranges of ARAT score and FMA-UE score, as presented in Hoonhorst (2015}, were used to approximate equivalent FMA-UE scores for the purpose of convenient comparison between the presented ARAT outcome scores and behavioral changes presented in previous publications. ARAT scores within the Upper-Limb category defined by baseline measures (Hoonhorst et al., 2015) were mapped to the FMA-UE score within the same category, rounded to the nearest whole integer, as FMA-UE measurements give scores in integer values.

Description of the Behavioral Outcome Measures

The primary outcome measure was the ARAT. The ARAT is a 57-point metric capable of assessing specific changes in upper limb function with sub-components for grasp, grip, pinch, and gross motor movement all of which sum to the total ARAT (Hsieh et al., 1998). The secondary outcome measures included the SIS, widely used to measure quality of life in stroke survivors, that consists of eight dimensions and a composite disability score (Vellone et al., 2015). The SIS is a 59-item patient-reported outcome measure, covering eight domains: strength (4 items), hand function (5 items), mobility (9 items), ADLs (10 items), memory (7 items), communication (7 items), emotion (9 items), and handicap (8 items). The domains are scored on a metric of 0–100, with higher scores indicating better self-reported health (Vellone et al., 2015). As it is possible the ARAT does not entirely capture the extent to which participants can functionally interact with their surroundings outside the laboratory, this subjective measure was chosen to support and record the participants' personal experience and opinion of their functional capacities relative to real-world application (Lang et al., 2017; Waddell et al., 2017). Self-report metrics are important for understanding the extent to which a participant is recovering UE motor

activities subjectively in a real-world setting (outside the testing room setting) (Stinear et al., 2017a; Stinear et al., 2017b). An additional secondary outcome measure was the 9HPT, which is a brief, standardized, quantitative test of UE function (Mathiowetz et al., 1985). The score for the 9HPT is an average of the two trials (Mathiowetz et al., 1985). Finally, a Smedley spring-type dynamometer tested the average grip strengths in pounds (lbs.) over three repeated trials per assessment to measure participant grip strength (An et al., 1980) (Malhotra et al., 2016).

Analysis of Outcome Measures

Data analysis of outcome measures examined four central relationships: (1) Change in outcome measure scores over time (Table 2); (2) primary outcome measure improvement rate differences between intervention and control (Table 3); (3) improvement rate differences in outcome scores between subjects who realized an increase in primary outcome (responders) and non-responders (Table 4); and (4) differences in covariates and outcome measurements between responders and non-responders (Table 4) for the purpose of discerning characteristic trends of those participants who best respond to this BCI intervention. It is important to note that for all responder analyses, participants who scored a perfect 57 total score at baseline and completion were excluded from the sample (n = 7 excluded) due to an inability to show improvement in primary outcome leaving n = 14 subjects remaining for all the responder sub-analyses. Likelihood ratio tests of linear mixed effect (LME) models offered rigorous analysis for each research question while paired and independent samples t-tests provided analysis of more general trends that LME may miss. Testing excluding the follow-up time period (time periods 1–3 of intervention) allowed for examination of direct effects of the BCI intervention while parallel analyses including the follow-up time point (time periods 1–4) gave insight into potential lasting effects of the BCI intervention.

Outcome Measures	Improvement Score Mean ± SD	LME Estimate ± SE	Covariates	*T*-Test *p* value	Time LME *p* value
Stroke Impact Scale (SIS)					
$SIS_{Hand\ Function}$	5.7 ± 16.4 (5.7 ± 13.9)	2.9 ± 1.9 (2 ± 1.1)	Severity, Gender	0.134 (0.180)	0.139 (0.07)
$SIS_{Mobility}$	8.7 ± 9.8 (7.2 ± 11.2)	4.4 ± 0.9 (2.6 ± 0.7)	Severity, Age, Chronicity, Gender	0.001*** (0.010) **	0.00001*** (0.00009)***
SIS_{ADL}	5.9 ± 10.1 (4.9 ± 9.6)	3.1 ± 0.2 (1.7 ± 0.8)	Severity, Concordance, Age, Gender	0.041* (0.035)*	0.0086** (0.054)*
$SIS_{Strength}$	7. 4 ± 13.9 (11.3 ± 12.1)	3.7 ± 1.6 (1.7 ± 0.8)	Severity, Chronicity, Gender	0.024* (0.001) ***	0.021* (0.00039)***
Grip Strength	3.8 ± 8.1 (2.1 ± 7.7)	1.9 ± 0.9 (1.0 ± 0.6)	Severity, Chronicity, Concordance	0.046* (0.246)	0.037* (0.062)
9-HPT_{Affect}	-5.9 ± 8.9 (-4.5 ± 5.3)	-2.9 ± 1.2 (-1.9 ± 0.7)	Chronicity	0.0081** (0.046)*	0.0201* (0.0118)**
Action Research Arm Test (ARAT)					
$ARAT_{Total}$	1.3 ± .2.4 (3.3 ± 4.9)	0.6 ± 0.3 (1.1 ± 0.3)	Severity, Gender, Chronicity, Gender	0.046* (0.020)*	0.275 (0.001)***
$ARAT_{Grip}$	0.1 ± 0.5 (0.9 ± 1.4)	0.03 ± 0.1 (0.3 ± 0.1)	Severity, Gender, Concordance, Chronicity, Age	0.582 (0.025)*	0.802 (0.0059)**
$ARAT_{Grasp}$	0.8 ± 1.6 (1.5 ± 3.6)	0.4 ± 0.3 (0.5 ± 0.2)	Severity, Gender, Concordance, Chronicity, Age	0.106 (0.163)	0.129 (0.03)*
$ARAT_{Pitch}$	0.4 ±1.6 (0.6 ± 1.5)	0.2 ± 0.2 (0.2 ± 0.1)	Severity, Gender, Concordance	0.289 (0.106)	0.215 (0.039)*
$ARAT_{Gross}$	0 ± 1.6 (0.3 ± 1.4)	0 ± 0.02 (0.1 ± 0.1)	Severity, Age, Chronicity, Concordance, Gender	1.00 (0.453)	1.00 (0.437)

Scores, Covariates, & *p* values are reported for *n*=21 participants during BCI intervention: Mean improvement scores between time points 1 & 3 (parentheses) indicates mean improvement scores between time points 1 & 4. The time LME *p* value is a *p* value for the likelihood test between two models differing only in the inclusion of time as a covariate
* p < .05, **p < .01, ***p <.001

Table 2: Summary of Outcome Measures During Assessment and Including Follow-Up of BCI Therapy.

Outcome measures used in all analyses included ARAT, Hand Grip Strength, and the 9HPT as well as SIS measures of Hand Function, Mobility, ADLs, and Strength of the hemiparetic side. For each analysis, and for each outcome measure utilized, ceiling scores (participants who recorded a maximum outcome score at baseline and completion for ARAT) were removed given the impossibility for measured improvement. On the other hand, floor scores (participant data that demonstrated a minimum outcome score at the intervention baseline measure) remained in all analyses akin to an intent-to-treat standard. Given this selection, the sample size across all data remained at n = 21 and n = 14 for the responder sub-analyses for most outcome measures. The outcome measurements with sample size adjustments following the above criteria include ARAT (n = 14 for both analyses) and SIShf (n = 20). Additionally, the sample size of 9HPTaffected (n = 9 overall, n = 2 in the responder dichotomization) was greatly reduced from the

original sample of 21 due to participants' inability to complete the task given the extent and severity of their UE impairment.

Independent samples t-tests utilized only DTG control data and ITG intervention data (neglecting the use of DTG intervention data) so as not to introduce an inter-subject dependence of the analyses. Meanwhile, the LME analyses used a random effect for subjects to account for the non-independence of the longitudinal data and used all subject time points. For each mixed model testing a specific outcome, relevant covariates to control for were chosen on stepwise regression analysis. For each outcome measure with the selected covariates, two nearly identical mixed models were created that differed only in the inclusion of a single covariate of interest. When examining how subjects' outcome scores changed with time, the covariate of interest was the time period (1, 2, 3, or 4) of interventional assessment. For comparing the intervention to control, both LME models included the independent effects of time and therapy type (control or intervention) and stringently tested for improvement rate differences by inclusion of an interaction term between time and type as the covariate of interest. Similarly, both models in the responder sub-analyses included independent effects of time and response (responder or non-responder) and stringently tested for improvement rate changes through an interaction term between time and response. Meanwhile, response was used as the covariate of interest to test if responders showed general differences in secondary outcome measures compared to non-responders. Finally, a similarly run generalized linear model (GLM) analysis examined potential significant covariates that helped predict whether a subject would become a responder through this BCI intervention. The specific covariates tested included stroke severity, chronicity, and concordance, as well as age, gender, and baseline ARAT scores. All mixed modeling analyses were completed in RStudio (Version 0.99.903 - © 2009-2016 RStudio, Inc.). The t tests were run using SPSS (Version22). Thresholds for significance were set a priori at $p \leq 0.05$ for all statistical analyses.

Post Hoc Rational: Dichotomizing Responders

Two groups, deemed 'Responders' and 'Non-Responders' (Snapinn and Jiang, 2007), were generated *post hoc* from this sample based on whether positive change in the primary objective measure of UE function was realized following BCI intervention (completion assessment score – baseline assessment score). The grouping of Responders vs Non-Responders is represented in Table 1 and Table 5. Table 1, the main demographics table, denotes Responders with asterisks in the Completion ARAT score column. Table 5 demonstrates relevant summary characteristic differences between the dichotomized groups.

The BCI System

BCI Software and EEG Hardware

The BCI system and intervention sequence were consistent with those previously described (Wilson et al., 2012) (Song et al., 2014c) (Remsik et al.) using BCI 2000 software (Schalk et al., 2004) version 2 with in-house modifications for input from a 16-channel EEG cap and amplifier (Guger Technologies) and integration with tongue stimulation (TDU) (TDU 01.30 Wicab Inc.) (Kaczmarek et al., 1991; Kaczmarek, 2011) and functional electrical stimulation (FES) of distal UE muscles (LG- 7500, LGMedSupply; Arduino 1.0.4) associated with grasping behavior.

Functional Electrical Stimulation

FES of the upper extremity was delivered using the LG-7500 Digital Muscle Stimulator (LGMedSupply, Cherry Hill, NJ, USA). Stimulus was conducted through a pair of 2" x 2" square electrodes placed securely on the affected forearm using highly conductive Electrolyte Spray. The electrodes were placed to facilitate either a grasping motion (finger flexion), or finger extension according to participant preference. Specific placement sites were superficial to digitorum superficialis to facilitate hand and finger flexion, or superficial to extensor digitorum communis to facilitate hand and finger extension. The natural absence of a flexor digitorum superficialis tendon to the fifth digit in some individuals was not considered by this study design. Stimulation was controlled through the PC using an Arduino Uno R3 (Adafruit Industries, New York, NY, USA) and a simple reed relay circuit, with the amplitude set to elicit observable muscle activation (e.g. finger grasping) without pain. The pulse rate of

the stimulation was set to 60Hz to produce tetanic contraction of the muscle; the pulse width was set to 150 μs. The input signal, initially set to zero, was adjusted by steps of 0.5 mA, unless the stimulation became uncomfortable for the subject. The device was never set to deliver an output greater than 5.0 mA.

Tongue Display Unit

In previous publications, the TDU has been described and its use in a BCI paradigm detailed (Schalk et al., 2004) (Kaczmarek, 2011) (Wilson et al., 2012). This BCI system uses the same TDU stimulation parameters as were previously reported (Wilson et al., 2012).

BCI Intervention Procedure

Familiarization With the BCI Device and Procedures The first BCI session was focused on assisting the participant to comprehend and engage the BCI device and protocol. Stroke survivors often present with a myriad of cognitive, affective, and physical impairments (Nair et al., 2015) (Stinear, 2016) and out of respect for individual participant needs and abilities, the researchers provide at outset an opportunity for a generous orientation rather than rigorous acquisition. During this preliminary session, the EEG cap, FES device, and TDU device were faithfully administered as described previously (Wilson et al., 2012). Participants were instructed before each session, and as needed, to aim for successful completion of BCI tasks and for each attempted movement to be performed to the participant's autonomously elected level of comfort, ability, and pleasure. The proposed design entails at least 10 runs for each closed-loop condition per session; however, enforcement discretion was encouraged until a participant demonstrated task comprehension.

Cursor Task and User Integration

In the closed-loop BCI intervention task, participants perform attempted actual hand movements in response to a left or right target cue displayed on a computer screen as a virtual ball-and-target. To accommodate initial movement capacity and recovery goals, best possible attempts at repeated hand grasping (finger extension and flexion) were used. Participants learn to control horizontal movement of a virtual ball displayed on the monitor by modulating their sensorimotor rhythm (SMR) activity (SMR activity represents Mu and Beta rhythm changes over the motor cortex – this process is indicative of

healthy normal brain electrophysiology of attempted movement) as they perform the task (Wilson et al., 2012). The SMR activity related to attempted left (or right) hand movements, as recorded by the EEG, is then translated into leftward (or rightward) ball movement via the BCI (Wilson et al., 2012). Mu and beta SMRs in human subjects (Muralidharan et al., 2011) are recorded exclusively over sensorimotor areas at frequencies of about 8–12 and 16–24 Hz (Pfurtscheller et al., 1997) (Birbaumer, 2006; Birbaumer and Cohen, 2007), with the source of human SMR in the sensorimotor regions following the homuncular organization of the motor and somatosensory cortical strip (Pfurtscheller et al., 1997) (Paz and Vaadia, 2004b; a; Paz et al., 2004). At the start of each intervention trial, a virtual target randomly appears on the left or right side of the screen. After 1 s, a virtual ball appears in the center of the screen, and the subject is instructed to move the ball toward the target by eliciting SMR modulation using attempted hand movement. For a trial to be considered successful, the ball must hit the target within 5 s of its appearance. Trials are aborted and considered unsuccessful if, after 5 s, the ball has not reached the target. The inter-trial interval is 3 s regardless of aborted or successful trial (Figure 2).

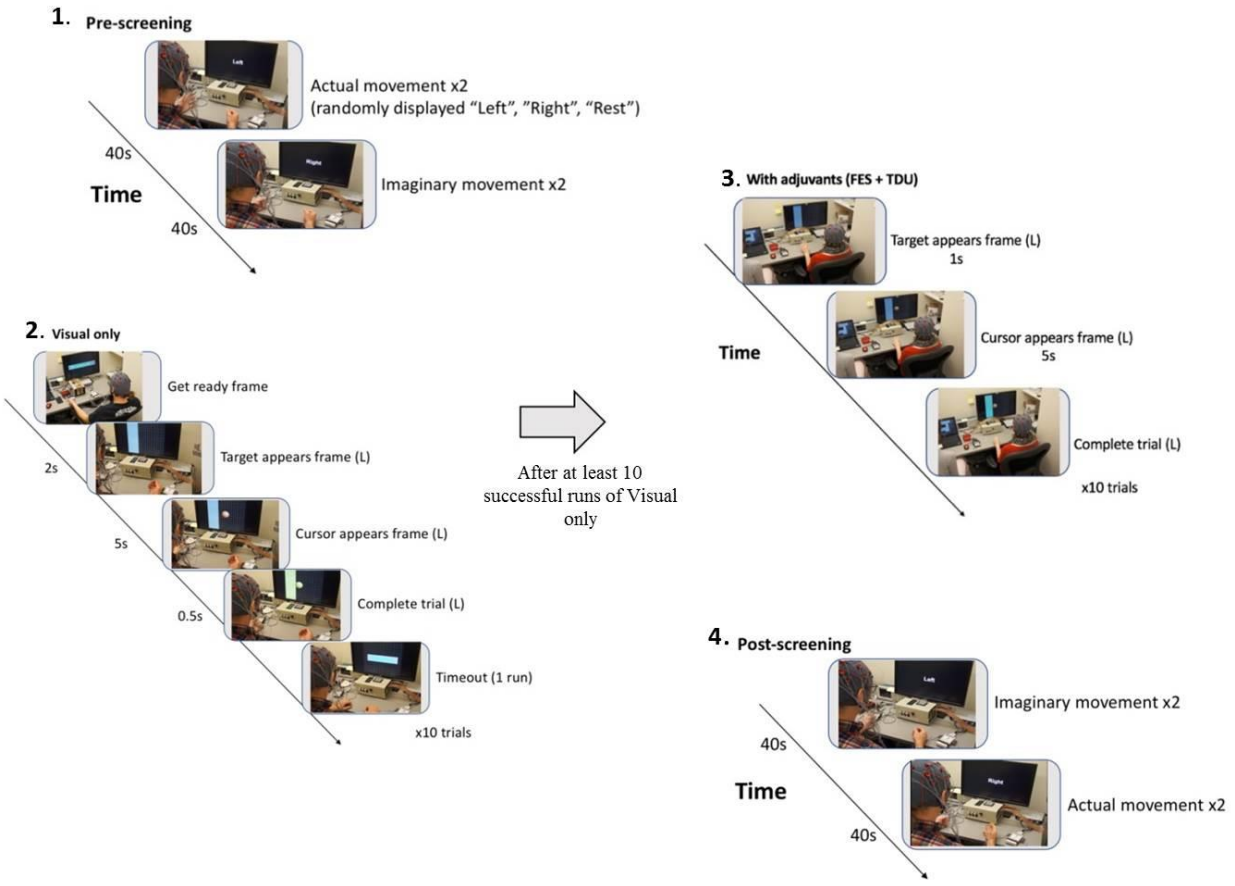


Figure 2: BCI intervention block design: (1) A pre-session open-loop screening task of two attempted and then two imagined grasping tasks (left, right, rest) is used to set control features (BCI classifier) for the forthcoming intervention task (Cursor Task). (2) The closed-loop cursor and target (visual only) intervention condition consists of at least 10 runs of 10 trials of attempted grasping movements for the purpose of guiding a virtual cursor (Ball) either left, or right as cued by the target (Goal) presentation on the horizontal edge of the screen. (3) Following 10 successfully completed runs of the visual only condition, adjuvant stimuli are added to enrich the feedback environment and facilitate volitional movement of the affected extremity (grasping). Subsequent runs are attempted at the preferred pace of the participant, completing as many runs as time allows. (4) With 15 min remaining in the 2-h intervention session, the participant is switched into the post-session open-loop screening task of two imagined and then two attempted grasping tasks (left, right, rest).

Adjuvant Stimulus Schedule

Following completion of at least 10 runs of the visual only BCI task described above, adjuvant FES stimulation was applied to the muscles of the impaired hand, and electro-tactile feedback (visual replication and supplementation) was presented when available through the TDU for the duration of the trials possible in a 2-h session. In this way, subjects might utilize visual feedback, muscle stimulation, and electro-tactile feedback (or visual replacement or supplementation in the case of uncorrected visual impairment) to monitor their task performance. FES-driven stimulation, however, was only applied to the impaired limb and concordant with both ball movement toward the impaired side, and the virtual target presenting on the impaired side. In this way, externally facilitated muscle stimulation never occurred while the subject was attempting to move the ball toward their unimpaired side.

RESULTS

Primary effect of BCI intervention

Of the n = 21 participants, 14 participants had room for improvement in the ARAT of which 64% (9/14) realized improved scores in the primary outcome measure (ARATtotal) from baseline to completion of intervention, both at immediate completion and/or 1-month post completion [Table 1]. 43% (6/14) had changes in the ARAT that are considered to meet significant ARAT specific thresholds (Four of these participants had Minimal detectable change (MDC) ≥ 3 (MDC = 3.0) and two of these participants had Minimally Clinical Important Difference ((MCID) ≥ 5.7 both at immediate completion and/or one-month post completion). The seven participants who had no room for improvement, or had a max score of 57 at ARAT, stayed at the same max level in ARAT both at immediate completion and one-month post completion.

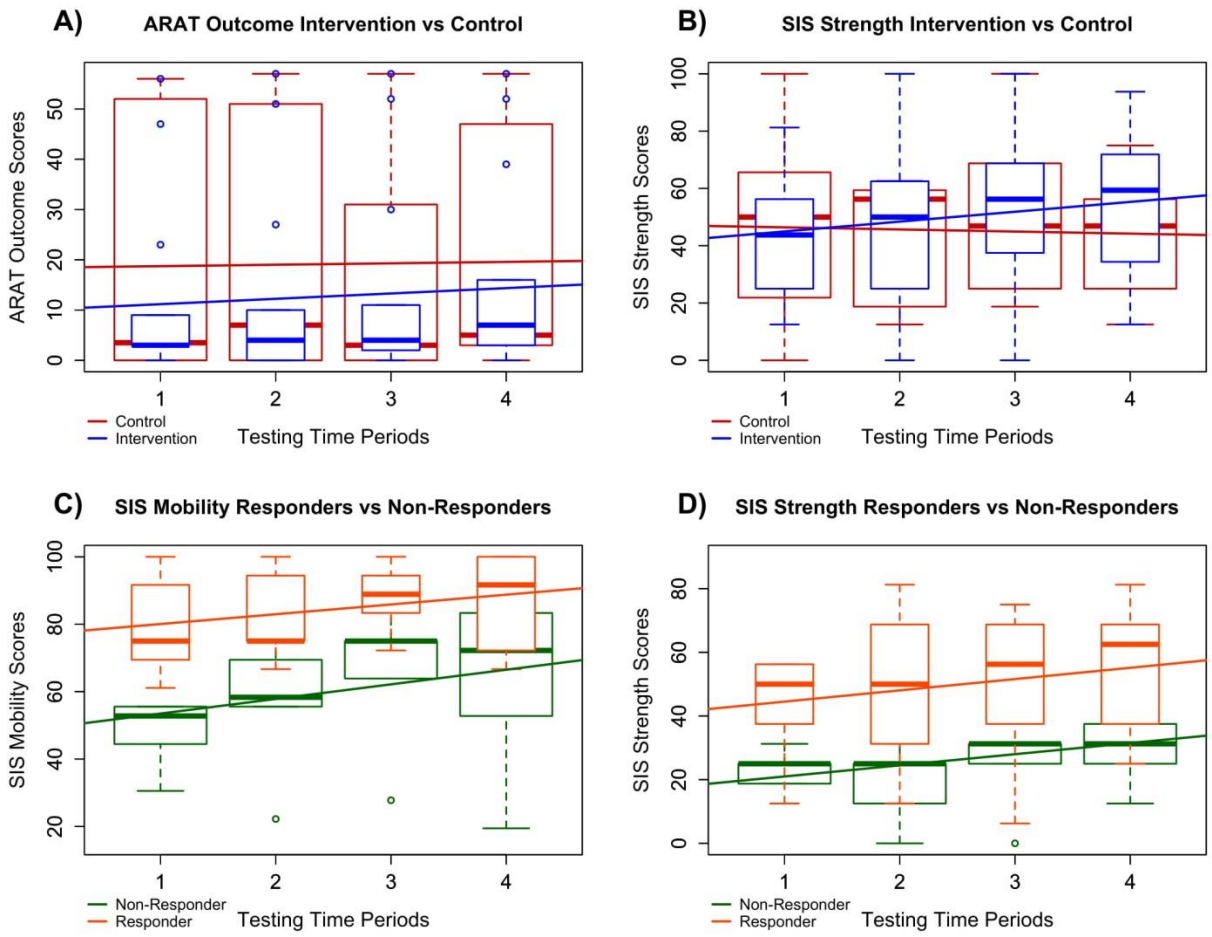


Figure 3: Intervention vs. Control and Responder vs. Non-Responder Plots: Four of the most notably significant relationships are plotted with boxplots of all patient data overlaid by simple linear best fit lines to depict general trends in the data. A and B specifically demonstrate differences in the data between all controls (in red) and all interventions (in blue) whereas C and D represent trends in the data between Responders (in orange) and Non-Responders (in green). A) Although the improvement rate in ARAT for subjects in intervention was not significantly higher than controls, participants in intervention did significantly improve over time, and the trend of the boxplot medians suggests a possible continuation of improvement through follow-up not present in the control period. B) Participants in Intervention significantly improved faster over time in SISstrength than those in the control period despite both groups starting at similar levels of ability. C) & D) Responders demonstrated significantly higher average SISmobility and SISstrength scores than Non-Responders. This suggests patients with lower SISmobility and SISstrength scores may not benefit from BCI intervention as well as those with higher scores.

Effect of Intervention Time on Outcome Scores

A paired samples *t* test found a significant effect of time on ARAT outcome improvement score (p=0.046). Secondary outcome measures found to have significant effect over time included SISmobility (p=0.001), SISadl (p=0.041), SISstrength (p=0.024), as well as Hand Grip Strength (p=0.046) and 9HPTaffected (p=0.0081) (Table 2).

Likelihood ratio tests of LME models over time periods 1-3 controlling for severity, gender, chronicity, and concordance did demonstrate a significant effect of time on ARAT outcome score improvement (p=0.02754) [Table 2]. Specifically, the full LME model revealed an estimate improvement rate of ARAT score by 0.64±0.28 (μ±SE) between time periods. In addition, the LME model found significance for the secondary outcome measures of SISmobility (p=0.00001), SISadl (p=0.008613), SISstrength (p=0.0212), Hand Grip Strength (p=0.0368), and 9HPTaffected (p=0.0201) while controlling for the most significant covariates as determined by forward stepwise regression [Table 2].

Including Follow-Up

A paired samples *t* test evaluated between baseline and follow-up demonstrated a significant effect of ARAT improvement score (p=0.020). Many secondary measurements at follow-up demonstrated similarly significant improvements including SISmobility (p=0.010), SISadl (p=0.035), SISstrength (p=0.001), and 9HPTaffected (p=0.046) [Table 2].

The likelihood ratio tests of the LME models across follow-up also demonstrated significant improvement in ARAT, controlling for severity, gender, chronicity, and concordance (p=0.0010) [Table 2]. The estimated improvement rate of ARAT score was 1.06 ± 0.31 (μ±SE) between time periods. The likelihood ratio tests also revealed significance among SISmobility (p=0.00009), SISstrength (p=0.00039), and 9HPTaffected (p=0.01178) (Table 2).

ARAT Improvement Rate Between Control & Intervention (Treatment Type) During Assessment Period

When testing between Control (n = 12) vs Intervention (n = 9) therapy types, the independent samples t tests did not find that subjects during intervention improved in ARAT outcome score at a significantly faster rate than controls. Additional measures via t tests found no significant differences between control and intervention from time points 1-3 [Table 3].

Outcome Measures	Control Improvement score Mean ± SD	Intervention Improvement score Mean ± SD	LME Estimate ± SE	Covariates	*T*-Test *p* value	Interaction LME *p* value
Stroke Impact Scale (SIS						
$SIS_{Hand\ Function}$	0.4 ± 10.6 (-0.9 ± 18.0)	3.8 ± 10.8 (5.6 ± 7.3)	2.6 ± 3.3 (2.1 ± 1.9)	Severity, Age, Time, Type	0.419 (0.180)	0.407 (0.278)
$SIS_{Mobility}$	5.1 ± 9.2 (2.7 ± 8.1)	11.7 ± 12.0 (8.6 ± 13.1)	1.8 ± 1.6 (1.5 ± 1.1)	Severity, Chronicity, Age, Gender, Concordance, Time, Type	0.197 (0.085)	0.237 (0.148)
SIS_{ADL}	3.5 ± 12.5 (0.2 ± 12.4)	9.2 ± 13.4 (5.0± 10. 3)	1.2 ± 2.1 (1.8 ± 1.3)	Severity, Concordance, Chronicity, Gender, Age, Time, Type	0.397 (0.156)	0.567 (0.175)
$SIS_{Strength}$	2.6 ± 17.1 (4.1 ± 18.3)	12.5 ± 8.8 (14.6 ± 10.3)	2.4 ± 2.8 (4.4 ± 1.7)	Severity, Chronicity, Gender, Time, Type	0.149 *(0.019)	0.379 **(0.012)
Grip Strength	-0.3 ± 6.4 (3.4 ± 11.0)	1.7 ± 5.0 (1.3 ± 3.6)	2.1 ± 1.5 (-0.3 ± 0.9)	Severity, Age, Time, Type (Chronicity)	0.526 (0.749)	0.163 (0.792)
9-HPT$_{Affected}$	-7.7 ± 12.4 (-2.5 ± 19.2)	-2.6 ± 4.8 (-3.8 ± 5.4)	0.9 ± 2.8 (-0.8 ± 1.8)	Time, Type (Chronicity)	0.826 (0.183)	0.741 (0.640)
Action Research Arm Test (ARAT)						
$ARAT_{Total}$	3.1 ± 4.08 (1.8 ± 3.8)	0.4 ± 2.1 (3.2 ± 5.5)	-0.8 ± 0.6 (0.5 ± 0.5)	Severity, Gender, Age, Chronicity, Time, Type, Concordance	0.228 (0.699)	0.154 (0.256)
$ARAT_{Grip}$	0.3 ± 6.5 (3.4 ± 11.0)	0.2 ± 0.4 (1.2 ± 1.6)	-0.5 ± 0.3 (0.1 ± 0.2)	Severity, Gender, Age Concordance, Chronicity, Time, Type	0.514 (0.195)	0.075 (0.458)
$ARAT_{Grasp}$	1.1 ± 2.1 (0.1 ± 0.4)	1.2 ± 1.9 (1.0 ± 3.5)	0.03 ± 0.4 (0.5 ± 0.3)	Severity, Gender, Age Concordance, Chronicity, Time, Type	0.579 (1.00)	0.949 (0.146)
$ARAT_{Pitch}$	0.8 ± 2.1 (0.3 ± 2.1)	-0.2 ± 0.4 (0.3 ± 0.8)	-0.2 ± 0.3 (0.2 ± 0.2)	Severity, Concordance,, Time, Age, Gender, Type (Chronicity)	0.391 (0.704)	0.508 (0.501)
$ARAT_{Gross}$	0.3 ± 0.5 (0.8 ± 1.2)	1.0 ± 1.9 (0.2 ± 0.5)	-0.2 ± 0.3 (-0.2 ± 0.2	Severity, Age, Concordance, Chronicity, Time, Type, (Gender)	1.00 0.252	0.46 (0.303)

Scores, Covariates, & *p* values are reported for *n*=21 participants during BCI intervention: Mean improvement scores between time points 1 & 3 (parentheses) indicates mean improvement scores between time points 1 & 4. Interaction LME *p* value is a *p* value for the likelihood ratio test between two LME models differing only in the inclusion of the time: type (where type is either intervention period or control) as a covariate.
* p < .05, **p < .01, ***p <.001

Table 3: Summary of Outcome Measures During Assessment and Including Follow-Up of BCI Therapy for Intervention vs. Control.

A likelihood ratio test controlling for severity, gender, age, chronicity, concordance, and the independent effects of time and therapy type (control or intervention) also did not find a significant effect of the specific interaction term between time and therapy type for ARAT outcome score (p=0.1543) [Table 3]. Similarly, improvement rates for secondary measurement outcome scores between intervention

and control from time points 1-3 were not significant while controlling with forward stepwise regression selected covariates and the independent effects of time and therapy type [Table 3].

Including Follow-up

The t test assessed at follow-up did not find a significant effect of ARAT outcome improvement score. However, there was a significant effect of SISstrength improvement score (p=0.019) [Table 3]. The likelihood ratio tests at follow-up for ARAT, controlling for severity, gender, age, chronicity, concordance and the independent effects of time and type was not significant (p=0.256) [Table 3 & Figure 2.A]. Like the t test, there was a significant effect between control and intervention for SISstrength (p = 0.0117) when controlling for severity, chronicity, gender, and the independent effects of time and therapy type [Table 3 & Figure 2.B].

ARAT Improvement Rate Between Responders & Non-Responders (Response Type)

During Assessment Period

When testing between Responders (n = 9) vs Non-Responders (n = 5), neither t tests nor likelihood ratio tests of generalized mixed effect models found the individual covariates of age, gender, chronicity, severity, concordance of strokes, or baseline ARAT scores to significantly predict a subject's ability to improve in ARAT outcome over the course of intervention. LME analyses demonstrated that, while controlling for severity, gender, chronicity, concordance, and the independent effects of time and response, Responders improved significantly faster than Non-Responders by 1.62±0.51 (μ±SE) points per time point through intervention [Table 4]. LME analyses further revealed significant positive differences between Responders and Non-Responders in SISmobility by intervention completion (p = 0.0002) and SISstrength (p=0.04995) [Table 4 & Figure 2.C]. Specifically, Responders demonstrated increased SISmobility scores of 19.63±5.75 (μ±SE) and increased SISstrength scores of 15.38±9.67 through intervention.

Outcome Measures	Responder Improvement score Mean ± SD	Non-Responder Improvement score Mean ± SD	LME Estimate ± SE		Covariates	*T*-Test *p* value	Interaction LME *p* value	Response LME *p* value
Stroke Impact Scale (SIS								
$SIS_{Hand\ Function}$	4.4 ± 21.4 (7.7± 19.54)	10.0 ± 11.8 (3.0 ± 4.5)	-2.8 ± 4.2 (0.4 ± 2.3)	6 ± 5.9 (7 ± 5.6)	Severity, *Time, Response* (Chronicity)	0.901 (0.544)	0.498 (0.877)	0.26 (0.179)
$SIS_{Mobility}$	9.2 ± 8.0 (8.0 ± 8.6)	12.8 ± 13.4 (11.6 ± 18.9)	-1.3 ± 2.3 (-1.4 ± 1.8)	19.6 ± 5.8 (18.6± 6.9)	Severity, Age, Chronicity, Concordance, Gender, *Time, Response*	0.382 (0.487)	0.564 (0.405)	0.000213*** (0.00155) **
SIS_{ADL}	8.6 ± 11.0 (6.3 ± 9.8)	10.0 ± 10.8 (9.5 ± 9.6)	-0.7 ± 3.1 (-2.0 ± 2.0)	10 ± 6.8 (9.7 ± 7.4)	Severity, Concordance, Gender, Age, *Time, Response*	0.295 (0.523)	0.819 (0.291)	0.0515 (0.0795)
$SIS_{Strength}$	6.2 ± 13.6 (11.8 ± 11.0)	2.5 ± 15.7 (10.0 ± 16.9)	1.9 ± 4.4 (0.04 ± 2.8)	15.4 ± 9.7 (14.8 ± 9.2)	Severity, Gender, *Time, Response*	0.255 (0.430)	0.661 (0.988)	0.049* (0.048)*
Grip Strength	3.0 ± 7.4 (1.7 ± 11.0)	1.0 ± 2.2 (1.3 ± 2.3)	1.0 ± 2.1 (0.4 ± 1.2)	6.1 ± 3.7 (5.5± 3.5)	Severity, Chronicity, Concordance, *Time, Response*	0.399 (0.864)	0.617 (0.766)	0.082 (0.095)
9-HPT Affected	—	—	—	—	—	—	—	—
Action Research Arm Test (ARAT)								
$ARAT_{Total}$	3.5 ± 5.2 (4.4 ± 6.2)	-0.8 ± 1.3 (1.4 ± 1.9)	1.6 ± 0.5 (1.2 ± 0.6)	4.4 ± 4.8 (5.1 ± 5.3)	Severity, Gender, Age Concordance, Chronicity, *Time, Response*	0.242 (0.204)	0.0026** (0.078)	0.239 (0.214)
$ARAT_{Grip}$	0.2 ± 0.4 (1.3 ± 1.4)	-0.2 ± 0.4 (0.4 ± 1.5)	0.2 ± 0.2 (0.3 ± 0.2)	0.9 ±1.1 (1.2 ± 1)	Severity, Gender, Chronicity, Concordance, *Time,, Response*	0.399 (0.208)	0.212 (0.158)	0.226 (0.099)
$ARAT_{Grasp}$	1.6 ± 1.8 (2.4 ± 4.6)	-0.2 ± 0.4 (0.4 ± 1.5)	0.9 ± 0.5 (0.6 ± 0.4)	1.9 ± 2 (2.4 ± 1.7)	*Time, Response* (Age, Chronicity)	0.347 (0.495)	0.09 (0.151)	0.236 (0.159)
$ARAT_{Pitch}$	0.7 ± 2.1 (1.1 ± 1.8)	0 ± 0 (0.3 ± 2.1)	0.04 ± 0.04 (0.4 ± 0.2)	1.0 ± 1.1 (1.1 ± 1.1)	Severity, Chronicity, *Time, Response*	1.0 (0.907)	0.322 (0.067)	0.296 (0.236)
$ARAT_{Gross}$	0.2 ± 1.5 (0.1 ± 1.6)	0.4 ± 1.8 (0.6 ± 0.9)	0.3 ± 0.4 (-0.1 ± 0.3)	0.8 ± 1.3 (0.4 ± 1.4)	Severity, Age, Concordance, Gender, *Time, Response* (Chronicity))	0.621 0.864	0.463 (0.727)	0.43 (0.509)

Scores, Covariates, & *p* values are reported for *n*=21 participants during BCI intervention: Mean improvement scores between time points 1 & 3 (parentheses) indicates mean improvement scores between time points 1 & 4. LME Estimate ± SE: Interaction LME | Response LME. Interaction LME *p* value indicates *Time* and *Response* independently as covariates. Response LME *p* value excludes *Time* and *Response* as covariates, and indicates response as a slope Interaction.
* p < .05, **p < .01, ***p <.001

Table 4: Summary of Outcome Measures During Assessment and Including Follow-Up for Responders vs. Non-Responder.

Including Follow-up

When testing between Responders (n = 9) vs Non-Responders (n = 12), neither *t* tests nor likelihood ratio tests of generalized mixed effect models found the individual covariates of age, gender, chronicity, severity, concordance of strokes, or baseline ARAT scores to significantly predict a subject's ability to improve in ARAT outcome through follow-up. LME analyses did not demonstrate a significant difference in improvement rates in ARAT between Responders and Non-Responders through follow-up while controlling for severity, gender, chronicity, concordance, and the independent effects of time and response (p=0.07821) [Table 4]. However, LME analyses did reveal significant positive differences between Responders and Non-Responders in SISmobility (p = 0.00155) and SISstrength (p=0.04828) through follow-up while controlling for the forward-step selected covariates [Table 4 & Figure 2.C].

Specifically, Responders demonstrated increased SISmobility and SISstrength scores of 18.59±6.88 and 14.80±9.23 (μ±SE) respectively through follow-up while controlling for the selected covariates [Table 4 & Figure 2.D].

Identifying patients for BCI intervention

These data suggest that particular participant characteristics may be associated with greater gains of functional capacity. The covariates of severity, concordance of strokes, age, gender and chronicity, within this limited sample size, may not, at this sampling, significantly predict whether a participant will improve in ARAT primary outcome scores due to BCI intervention. However, increased SISmobility and SISstrength scores do significantly help predict response outcome [Table 4]. It is further possible that other outcome scores relatively close to significance ($p \leq 0.1$), such as SISadl and Hand Grip Strength [Table 4], may prove significant with an increase in sample size. Additionally, although gender, chronicity, severity or concordance did not significantly predict if a participant would become a Responder, 73% (8/11) of chronic and 100% (2/2) of mild participants who had room for ARAT improvement became Responders. Responders to this intervention schedule were, like the larger cohort sample, a heterogeneous group and included survivors with severe motor impairment of non-dominant hand [Table 5] as measured post stroke. It may be possible to extrapolate upon these data, strengthened by systematic review of existing literature, to identify patients prepared to realize optimal recovery outcomes with BCI intervention.

Response	Participants	Age (years) Mean ± SD	Females (Males)	Acute (Chronic)	Mild (Severe)	Concordant (Non-Concordant)
Responder	9	62.6 ± 14.3	5 (4)	1 (8)	2 (7)	2 (7)
Non-Responder	5	58.3 ± 12.9	3 (2)	2 (3)	0 (5)	0 (5)
Total	14	61.1 ± 13.5	8 (6)	3 (11)	2 (12)	2 (12)

Concordant strokes are classified as those predominantly affecting the preferred arm as assessed by the Edinburgh Handedness Inventory [30]. Individual Responder and Non-Responder demographics are highlighted on ARAT outcome denoting the Responders.

Table 5: Demographic Distribution by ARAT Score Response

DISCUSSION

Prescribing BCI as UE Therapy

Brain–computer interface intervention can impact functional motor capacities of the impaired UE (Remsik et al., 2016), and in this sample, primary outcome measurements of distal UE function did significantly improve from baseline to completion as well as baseline to follow-up (Table 2). Results also suggest the delayed therapy condition utilized in this cross-over controlled design did not adversely affect UE impairments in individuals randomized into the DTG. Participants in intervention showed greater rate of change compared to control (Figure 3A) as well as greater average gains by completion. However, these differences were not statistically significant. Insufficient power, especially following the removal of ceilings, as well as the duration of specific neural plastic changes (weeks, months, or longer) (Jones, 2017), may contribute to this lack of significant differences.

Although BCI intervention appears to lead to functional reorganization of the central nervous system, or brain (Caria et al., 2011) (Song et al., 2014c) (Song et al.) (Paz and Vaadia, 2004a) (Cervera et al., 2018), it is not unreasonable to suggest that more time in therapy is needed for these CNS changes to manifest as measurable, clinically relevant changes in UE behavior. This possibility may explain the delay in primary outcome improvement between baseline and midpoint medians (2–3 weeks apart) compared to the differences between baseline and completion or even the middle time point and completion (Figure 3A). This assumption is supported by the continued improvement between midpoint and follow-up for those in intervention, a change which is not observed in the control group (Figure 3A). This delay of 2–3 weeks of the larger primary outcome score change is also consistent with a similar BCI therapy research design (Li et al., 2014). Further analysis about the rate of change at various time points is needed.

Mean projected FMA-UE changes from baseline to follow-up in this sample (5.4) are comparable to improvements in FMA-UE baseline to completion score changes (Cervera et al., 2018) in other published experimental BCI intervention studies. Subchronic patients generally experience greater

therapeutic effects of BCI interventions than do chronic participants (Cervera et al., 2018), and a similar limiting relationship may exist between mild and severe UE impairment patients (Nudo and Hillis, 2010) (Stinear and Byblow, 2014). Such trends may account for some differences between the presented projected FMA-UE score changes estimated from this sample (mean change of 2.2 and 5.4 at completion and 1-month post-completion, respectively) (Table 1), which are potentially labored by the heterogeneity of time since stroke and level of physical impairment post-stroke, and greater changes reported in similar studies (Li et al., 2014) (Kim et al., 2016) by other groups. For example, Li (2014) (n = 7) demonstrated a 12.7 FMA-UE change, however with a sample of subjects that was much less chronic (all chronicity ≤ 6 months) than those participants examined herein (Li et al., 2014). Similarly, Kim (2016) (n = 15) saw a 7.87 change in FMA-UE scores, however on average (baseline μFMA−UE = 26.8), those subjects had less severe strokes (Kim et al., 2016) than the participants in this sample. In general, most BCI intervention studies remain underpowered and inadequately constrained (Cervera et al., 2018), presenting threats to both internal and external validity.

The results of this study suggest that SISmobility and SISstrength may be important factors to consider when designing or prescribing BCI regimes as higher scores were significantly indicative of increased likelihood for treatment success. While still unclear, other factors that may also play predictive roles in BCI interventional motor recovery include, but are not limited to, Hand Grip Strength and SISadl scores, as well as stroke chronicity and severity. While insignificant due to the small sample size, the large proportions of chronic and mild patients who became responders, 73% (8/11) and 100% (2/2), respectively, does follow previously reported trends (Caria et al., 2011) (Ang et al., 2013) (Young et al., 2014a) (Ang et al., 2015) (Remsik et al., 2016). The fact that BCI intervention appears to be able to specifically benefit chronic patients is especially interesting as many stroke patients reach a functional recovery plateau by completion of standard of care treatment (Wolf et al., 2006) (Wolf et al., 2010) (Dromerick et al., 2009) (Nudo and Hillis, 2010). The heterogeneity of these data and relatively small

sample size may limit the external validity of all reported trends as well as limit the realization of other important predictors.

To date, the literature exploring the behavioral and rehabilitative implications of BCI treatments remains underpowered. Nonetheless, this body of research has shown rapid growth in the last decade and a half (Remsik et al., 2016) (Bundy et al., 2017) (Cervera et al., 2018). Research assessing which presenting stroke patients will profit most from BCI treatments remains mostly inconclusive. However, increased microstructural integrity of the ipsilesional posterior limb of the internal capsule (PLIC) has been correlated with greater motor recovery from BCI therapy (Song et al., 2014b) (Song et al.). Similarly, Young (2016) demonstrated that changes to the integrity of the contralesional corticospinal tract (CST) during BCI therapy correlates to behavioral improvement scores for ARAT and 9-HPT. Thus far, most BCI treatment studies have observed participants in the chronic stage of stroke. As BCI is still a relatively new concept for treatment of UE paresis, it is possible that the majority of individuals participating in BCI research have exhausted standard clinical care. Thus, samples may be weighted disproportionately by participants with chronic persistent UE motor disability. It is also possible that the therapeutic impact of BCI intervention is dependent on several factors (i.e., residual motor capacity, lesion volume, and time since stroke) which should be considered before BCI treatment is prescribed (Stinear and Byblow, 2014). A forthcoming intent to treat analysis of this study should help address some of these unanswered questions in a more robust manner.

Motivational Influences of BCI Use

Changes in primary outcome scores (ARAT) during treatments suggested that this BCI design may deliver moderate objective positive UE motor changes, as seen in the 64% (9/14) of participant (out of those who had room for improvement) “Responders” who completed the BCI treatments protocol as designed. 43% (6/14) had changes in the ARAT who are considered to meet significant ARAT-specific thresholds [four of these participants had MDC of at least 3 (MDC = 3.0 (Lyle, 1981)) and two of these participants had MCID of at least 5.7 both at immediate completion and/or 1-month post-completion.

Additionally, the largest positive changes compared to baseline in ARAT were observed 1-month post treatment for a few participants. This might suggest that continuation of biological and behavioral recovery mechanisms induced by BCI systems may remain active in participants beyond their time in the lab setting.

Limitations

Suitability of Dichotomized Responder Analysis as a Sufficient Measure of Clinical Importance of Treatment Effects

A significant portion of this publication is dedicated to an analysis of participants according to post hoc dichotomized assignment by main effect in the primary outcome. Responder analyses are challenged by several inherent limitations (Snapinn and Jiang, 2007). First, the arbitrariness of a "responder" threshold value levies a substantial cost as dichotomization decreases efficiency and increases sample size requirements (limited power relative to analysis of the original selection). Further, the motivation for a responder analysis is to assess clinical relevance (to ensure clinical relevance of treatment effect), and as clinical relevance is ubiquitous with every clinical trial and setting, such logic may be seen as inherently circuitous. Beyond the inherent shortcomings of a post hoc responder analysis, this study was constrained by heterogeneity in many covariates including lesion location, level of impairment, age, gender, and time since stroke among the participants studied. Certainly, greater power is needed to adequately generalize results to a more adequate standard.

Nature of the Academic Research Environment

This is an ongoing study in its seventh year of data acquisition and enrollment. Multiple different project personnel have undergone and supervised the staffing, training, and data acquisition of this trial during its course. The authors work hard to best minimize differences in acquisition of study measures through extensive and repeated training of personnel.

CONCLUSION

Both primary (ARAT) and secondary (SISmobility, SISadl, SISstrength, Hand Grip Strength, and 9HPTaffected) outcome measures were significantly improved over the course of this BCI interventional therapy. For SISstrength scores specifically, participants in intervention demonstrated significantly

increased improvement rates through follow-up as compared to controls while controlling for severity, chronicity, gender, and the independent effects of time and therapy type as measured through likelihood ratio tests of LME models. None of the analyses revealed any significant negative effect of delaying BCI treatments for participants. This particular result may be attributed to the chronicity of most of the recruited participants ($n = 16 \geq 1$ year, $n = 17 \geq 6$ months) since patients typically reach a functional plateau before the chronic phase of stroke and are not expected to realize a large degree of change, rehabilitative or otherwise, to their UE motor capacity. This particular study did not reveal significant differences between those who demonstrated improvement in ARAT outcome and those who did not in terms of age, gender, chronicity, severity, or concordance of stroke impairment suggesting that the BCI intervention design may be suitable for a large range of patients. However, 8/11 chronic, and both mild, participants with room for ARAT score improvement achieved "responder" designation, and the explicit capacity of BCI treatments to assist chronic (and mild) stroke patients, even after they have reached a functional plateau, is reported in other literature (Caria et al., 2011) (Young et al., 2014a) (Ang et al., 2015) (Remsik et al., 2016). Despite statistical limitations of the heterogeneity of the relatively small sample size in this study, those who responded to the BCI intervention did have significantly higher self-reported SISmobility and the SISstrength scores through follow-up. These findings may suggest that particular measures can assist in the prescription of a BCI intervention regimen necessary for an individual participant, as well as aid in the prediction and measurement of BCI interventional success as assessed by primary outcome measures of capacity and performance, like the ARAT.

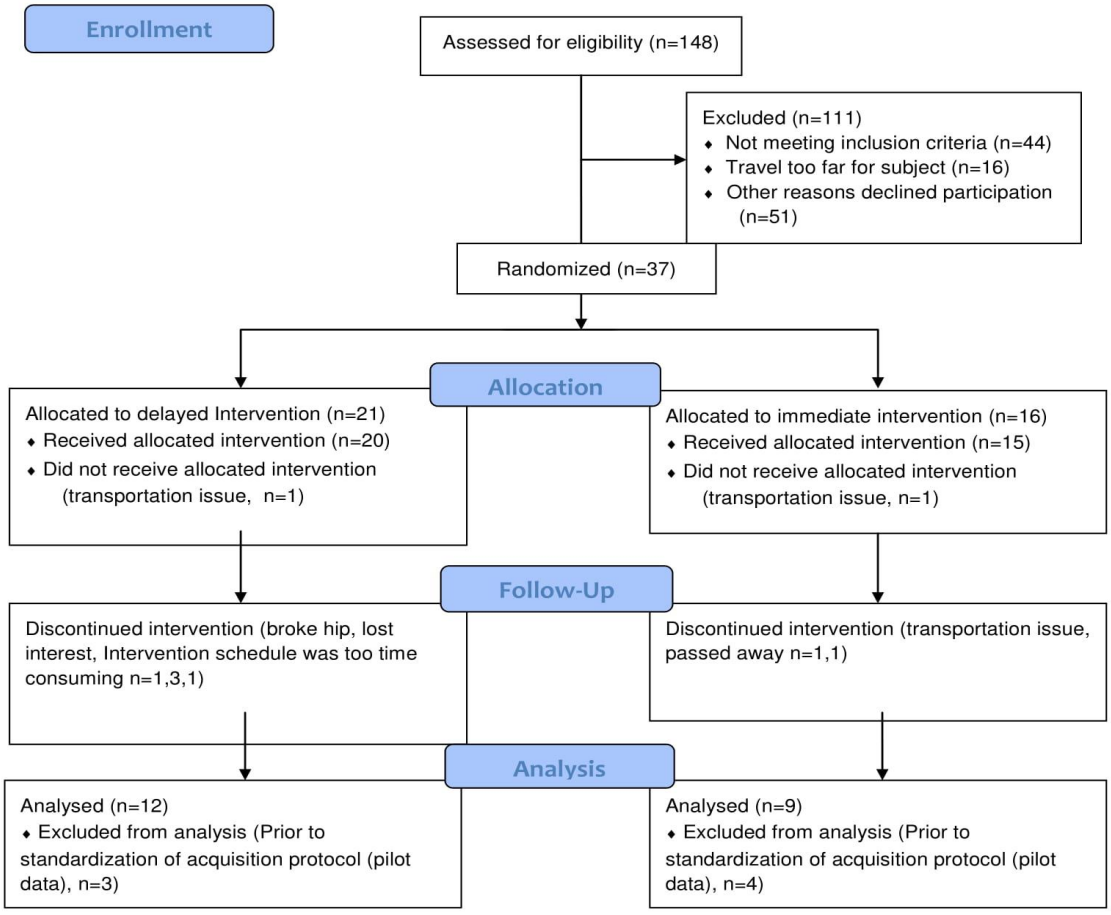
Additional research is required to identify how BCI intervention dose–response relationships are influenced by the various potential classifications of stroke survivors. It is quite possible that prescribing BCI intervention as a one-size fits all treatment for UE motor impairment may not be an ideal approach for this rehabilitative technology. Rather, these data suggest that at least some outcome measures, along with stroke severity and chronicity, may prove valuable in determining if BCI treatments could be effective for a stroke survivor with persistent UE paresis. Therefore, patients receiving BCI treatments in

future research or clinical contexts might benefit most from a treatment regimen tailored to the individual's presenting performance capacity as measured by the easily administered and scored SIS. Supplementary outcome measures (both objective and self-reported), impairment characteristics, and treatment goals should all be taken into account when designing a BCI intervention for a potential participant. Future studies should seek to more thoroughly examine the effects of patient characteristics on BCI effectiveness and examine how to deliver targeted treatments based on individual impairments and treatment goals in a concerted effort to maximize rehabilitative effect with similar BCI intervention strategies.

SUPPLEMENTARY MATERIALS
CONSORT Flow diagram

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT Behavioral Flow Diagram



Chapter 4

Ipsilesional Mu Rhythm Desynchronization and Changes in Motor Behavior Following Post Stroke BCI Intervention for Motor Rehabilitation

Remsik AB, Williams L Jr, Gjini K, Dodd K, Thoma J, Jacobson T, Walczak M, McMillan M, Rajan S, Young BM, Nigogosyan Z, Advani H, Mohanty R, Tellapragada N, Allen J, Mazrooyisebdani M, Walton LM, van Kan PLE, Kang TJ, Sattin JA, Nair VA, Edwards DF, Williams JC and Prabhakaran V (2019) Ipsilesional Mu Rhythm Desynchronization and Changes in Motor Behavior Following Post Stroke BCI Intervention for Motor Rehabilitation. *Front. Neurosci*. 13:53. doi: 10.3389/fnins.2019.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at:

https://www.frontiersin.org/articles/10.3389/fnins.2019.00053/full#supplementary-material

ABSTRACT

Loss of motor function is a common deficit following stroke insult and often manifests as persistent upper extremity (UE) disability which can affect a survivor's ability to participate in activities of daily living. Recent research suggests the use of brain–computer interface (BCI) devices might improve UE function in stroke survivors at various times since stroke. This randomized crossover-controlled trial examines whether intervention with this BCI device design attenuates the effects of hemiparesis, encourages reorganization of motor related brain signals (EEG measured sensorimotor rhythm desynchronization), and improves movement, as measured by the Action Research Arm Test (ARAT). A sample of 21 stroke survivors, presenting with varied times since stroke and levels of UE impairment, received a maximum of 18–30 h of intervention with a novel electroencephalogram-based BCI-driven functional electrical stimulator (EEG- BCI-FES) device. Driven by spectral power recordings from contralateral EEG electrodes during cued attempted grasping of the hand, the user's input to the EEG-BCI- FES device modulates horizontal movement of a virtual cursor and also facilitates concurrent stimulation of the impaired UE. Outcome measures of function and capacity were assessed at baseline, mid-therapy, and at completion of therapy while EEG was recorded only during intervention sessions. A significant increase in r-squared values [reflecting Mu rhythm (8–12 Hz) desynchronization as the result of attempted movements of the impaired hand] presented post-therapy compared to baseline. These findings suggest that intervention corresponds with greater desynchronization of Mu rhythm in the ipsilesional hemisphere during attempted movements of the impaired hand and this change is related to changes in behavior as a result of the intervention. BCI intervention may be an effective way of addressing the recovery of a stroke impaired UE and studying neuromechanical coupling with motor outputs.

INTRODUCTION

Stroke

Stroke is a leading cause of acquired adult long-term disability in the United States (Benjamin et al., 2019) and occurs when blood supply to the brain is compromised, leading to functional deficits that may affect activities of daily living (ADLs). Approximately 85% of patients who suffer and survive a new or recurrent stroke in the United States each year require rehabilitation. Six months post-stroke, nearly 50% of survivors have some residual motor deficits (Benjamin et al., 2019). By 2050, stroke burden on the United States economy will approach $2.2 trillion (Benjamin et al., 2019). Despite advances in acute stroke care, the estimated direct and indirect costs of stroke continue to escalate and are disproportionally associated with long-term care and rehabilitation (Benjamin et al., 2019). Current standard of care seems insufficiently developed to treat long-term motor deficits, potentially further burdening patients as untreated motor impairment can lead to deconditioning and underutilization of the affected upper extremity (UE), a consequence deemed, learned non-use (LNU) (Schaechter, 2004).

Customary Care and the Opportunities for Improvement

Several rehabilitation techniques are traditionally used for stroke recovery including conventional physical-occupational- speech therapies, provided in acute care settings as well as newer motor therapies such as constraint-induced movement therapy (CIMT), robot-aided therapy, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and virtual reality (VR) (Kollen et al., 2006) (Lindenberg et al., 2010a) (Fleet et al., 2014) (Laver et al., 2015) (Song et al., 2015b) (Babaiasl et al., 2016) (Smith and Stinear, 2016). Importantly, a much different level of evidence exists for CIMT and traditional therapies than experimental therapies such as tDCS and VR-based approaches. Existing pharmacological treatments, Botox injections for example, and traditional physical therapy methods primarily serve to treat symptoms associated with stroke (Benjamin et al., 2019) and may not focus on bringing about basic changes to the underlying impaired brain function associated with relevant post-stroke pathologies. Patients with UE motor impairment traditionally receive rehabilitation regimens that

involve passive, repetitive movement of the impaired limb without directly linking brain activity to these movements (Dromerick et al., 2009). Whereas passive movement repetition can be an effective rehabilitation strategy, recovery can be slow, and suboptimal. In contrast, linking brain activity to movement is important for motor skill learning (e.g., walking, running, throwing, writing, etc.) and the formation of central to peripheral connections. Leveraging this innate and robust motor learning circuitry, harnessing brain plasticity (Thakor, 2013), may be the next step toward improve patient outcomes.

Motor Recovery

Research suggests that motor recovery post-stroke, similar to motor learning, requires specific internal and external environmental conditions (Power et al., 2011). For example, lesion load is a limiting factor as sufficient existing neural architecture is needed for motor recovery to occur (Power et al., 2011). Recovery likely manifests either by the return of function to surviving neural architecture, or via neural reorganization and neural network remapping of proximal (i.e., near-by) neural architecture (Jones, 2017). Perhaps such processes may even be related. If neuroplasticity in the motor system, though likely attenuated by age, is continuous over the life course (Power et al., 2011), long-studied learning theories such as Hebbian plasticity and classical conditioning might be better integrated in treatment designs to aid recovery of stroke impaired UE motor capacities (Power et al., 2011) (Remsik et al., 2016). The incorporation of neurorehabilitation techniques has yielded operational clinical therapies and devices (Pfurtscheller et al., 1997) (Pfurtscheller et al., 2005a) (Neuper and Pfurtscheller, 2001) (Pineda, 2005) (Felton et al., 2007) (Schalk et al., 2008) (Power et al., 2011). As a number of existing approaches suffer from issues of high cost, passive movement repetition, large equipment, personnel and time constraints it is crucial efforts are made to pursue more expedient and efficacious means of rehabilitation, improve our quality of care, and better serve our survivors.

Sensorimotor Rhythms

Human brain rhythms associated with motor output, sensorimotor rhythms (SMRs), are recorded superficial to the motor and somatosensory cortical strip of the brain (electrode sites C3 and C4) and originate according to homuncular organization (Pfurtscheller et al., 1997) (Birbaumer, 2006; Birbaumer

et al., 2006). At the motor cortical strip (generally, Brodmann areas 3–6), each brain hemisphere desynchronizes with imagined, attempted, and also preparation of movement. This phenomenon is known as event-related desynchronization (ERD). Specific frequency bands have been associated with specific aspects of event-related motor behaviors (Pfurtscheller et al., 1997) (Pfurtscheller et al., 2005a) (Felton et al., 2007) (Schalk et al., 2008) (Song et al., 2014c) (Young et al., 2014a). In normal effortful movement, Mu rhythms of the contralateral cortex are desynchronized and attenuated (ERD) as movements are planned and executed (Pfurtscheller et al., 1997). This is followed by an increased presence of Beta rhythm ERD in the contralateral motor cortex which is associated with the later stages of motor command output and control (Pineda, 2005). After the completion, or at the cessation of movement, the SMRs in Mu and Beta frequency bands synchronize (ERS). ERD and ERS were key elements in the development and use of early BCIs for the rehabilitation of motor functions (Pfurtscheller et al., 1997) (Pfurtscheller et al., 2005a) (Nam et al., 2011). The early designs confirmed that ERD or ERS in specific spatial areas and neural networks (e.g., thalamocortical networks, frontoparietal networks) associated with a task or triggered events can be utilized to control a device or output command (Pfurtscheller et al., 1997) (Neuper and Pfurtscheller, 2001).

Mu and Beta sensorimotor rhythms (SMRs) in human subjects are recorded exclusively over sensorimotor areas at frequencies of about 10–20 Hz (Pfurtscheller et al., 1997) (Birbaumer, 2006). Two basic strategies in SMR-based control have been introduced for motor rehabilitation in stroke patients: motor imagery (Wolpaw et al., 1991) (Ortner et al., 2012) (Irimia et al., 2016) and attempted movement-based approaches (Wolpaw et al., 1991) (Schalk et al., 2004). Either approach utilizes essentially overlapping neural architecture to provide input signals (electrophysiological recordings by the EEG cap) to the BCI. The authors of this study designed the protocol to utilize attempted hand movements during the intervention according to the logic that a motor therapy intended to restore volitional motor function of the affected UE should utilize voluntary attempted movements of that impaired hand in a continuous effort to improve the participant's UE capacity and performance.

Brain–Computer Interface (BCI) and Electroencephalography for Assistive Design

Noninvasive brain–computer interfaces (BCIs), which utilize ancillary adjuvant peripheral devices and electrical muscle stimulation, as well as invasive BCI approaches with electrodes implanted in the skull, have been introduced (Wolpaw et al., 1991) (Leuthardt et al., 2004) (Schalk et al., 2004) (Schalk et al., 2008) (Vaughan et al., 2006) (Felton et al., 2007) as contemporary intervention and rehabilitation techniques following neural disease or trauma, such as stroke. Devices similar to what was utilized in this research are controlled by input signals generated by scalp electroencephalographic (EEG) recordings from electrodes superficial to the sensorimotor cortices. EEG signals associated with various components of voluntary movement are identified and translated into a device command or specified output (Pfurtscheller et al., 1997) (Felton et al., 2007) (Schalk et al., 2008) (Wilson et al., 2012), like activation of an FES pad (Song et al., 2014c) (Young et al., 2014a). BCIs can monitoring volitional modulation of electrical brain rhythms and execute an augmentative, facilitative, or rehabilitative command in the presence or absence of such signals.

Adjuvants

In this study, EEG driven BCI was linked to tongue stimulation (TS) via a Tongue Display Unit (TDU) (Kaczmarek, 2011) (Wilson et al., 2012) (designed as a visual supplementation for any participant with visual impairments) and FES, which can act not only as therapeutic adjuvants but, when tied to intent- to-move brain signals, also provide users with multi-modal feedback as a form of monitoring and reward for producing relevant brain activity patterns (SMR modulation) during tasks. Adjuvant stimulation may not only aid execution of the motor plan by causing the contraction of the impaired UE musculature but may also help the user learn new movement strategies for the impaired extremity. Adjuvant-induced proprioceptive and general afferent inputs to the motor system complete the BCI design's replication of the native neurobiological closed- loop motor system. Such adjuvant-aided volitional movement may not only make a movement possible but also contribute ancillary components for motor learning. Rewards of tactile, kinesthetic feedback to the system and the visual revelation of a

previously impaired appendage now voluntarily animated may prove powerful (Popovic et al., 2009) (Howlett et al., 2015) reinforces.

Evidence

Growing evidence from our lab and other groups (Daly and Wolpaw, 2008) (Daly et al., 2009) (Caria et al., 2011) (Muralidharan et al., 2011) (Ang et al., 2013) (Várkuti et al., 2013b) (Bundy et al., 2017) suggest that noninvasive EEG-BCI-FES systems hold potential for facilitating recovery in the chronic phase after stroke by linking central nervous system (CNS) commands, or brain activity, with distal motor effectors (the manifestation of the motor plan via trained muscle synergies) of the peripheral nervous system (PNS). Integration of the aforementioned command with facilitated movements within strict reinforcement constraints (e.g., task accuracy: drop the cup, move the ball or not) might thereby better harness neuroplastic capacities leading to functional gains in recovery for individuals with stroke related hemiparesis. Previous studies suggest that change in the pattern of brain activity linked to attempted movements of the affected hand contributes to motor re-conditioning and induces brain plasticity or reorganization which, if properly directed and reinforced, should lead to improvement in a stereotyped motor function of interest (Daly et al., 2009) (Caria et al., 2011) (Muralidharan et al., 2011) (Várkuti et al., 2013a). This is of special importance for patients in the chronic phase (generally >6 months post stroke) of recovery who may have little to no residual function in the affected arm, in addition to learned compensatory motor strategies (Muralidharan et al., 2011). Given that these participants have also likely exhausted other forms of intervention available to them through standard healthcare channels, it is imperative to explore novel intervention technologies that show promise in this population.

Overview of This Study

It was hypothesized that (1) the EEG-BCI-FES intervention sessions would result in increased hemispheric desynchronization levels of Mu (8–12 Hz) rhythm and, or Beta (18–26 Hz) band signals over the ipsilesional motor cortices, as reflected by increased r-squared values (i.e., lower power in the impaired hand movement trials compared to rest), and (2) changes in functional connectivity (coherence)

are greatest in the affected contralateral (ipsilesional) motor cortex and, over time, are associated with beneficial behavior and quality of life improvements as measured by objective and subjective measures of upper extremity motor function and activities of daily living. This interim analysis, of the larger ongoing prospective randomized crossover-controlled clinical trial, seeks to determine whether greater desynchronization of motor related SMRs in the ipsilesional hemisphere during attempted movements of the impaired hand are related to changes in behavior as a result of intervention.

MATERIALS AND METHODS

Participants and Design

Ethics Statement

Participants were recruited from the greater Madison, WI, United States area as part of an on-going prospective randomized, cross-over controlled design stroke rehabilitation study investigating interventional BCI targeting UE motor function. This study is approved by the University of Wisconsin Health Sciences Institutional Review Board (Study ID 2015- 0469); all subjects provided written informed consent upon enrollment.

Recruitment and Enrollment

This on-going study, registered with ClinicalTrials.gov (study ID1 NCT02098265) (https://clinicaltrials.gov/ct2/show/NCT02098265), employs an open call for participants with a wide range of (1) UE hemiparesis resulting from stroke, (2) time-since- stroke, (3) stroke type, (4) lesion location, (5) number of previous strokes, (6) and stroke severity. Subsequent to informed, written consent, stroke survivors were randomized by permuted-block design accounting specifically for gender, stroke chronicity, as well as severity of motor impairment as measured by the Action Research Arm Test (ARAT) (Lang, 2008) (n = 21, mean age = 61.6 years ± 15.3 years, 12 female, 13 right lateralized lesion, mean chronicity = 1127 days ± 1326.5 days, median chronicity 588 days, 11 with severe UE motor deficit, mean baseline ARAT score of impaired side = 26.6 ± 26.1). Chronicity is measured as time since stroke, in days, to baseline measurement day. Participant characteristics are displayed in Table 1. This interim analysis of the larger ongoing study seeks to elucidate the electrophysiological consequences and

associations of BCI participation, and the authors focus specifically on the behavioral (primary outcome) associations in another manuscript published in tandem with this effort (Remsik et al., 2018).

Participants	Age Years	Chronicity Days	Severity	Clinical Cause Lesion Location	Baseline ARAT	Completion ARAT	FollowUp ARAT	ARAT Change
1	47-51	160	severe	L-Lateral Medulla	3	2	7	-1 (4)
2	49-53	490	severe	R-MCA Stroke	3	4	8	*1 (5)
3	76-80	658	mild	Leg/Periventricular White, MHR	57	57	57	0 (0)
4	67-51	2723	severe	R-PLIC Putamen	23	40	39	*17 (16)
5	81-85	580	mild	Cerebellar Vermis	47	52	52	*5 (5)
6	73-77	197	severe	R-Prefrontal, Midfrontal, Temporal	0	0	3	0 (3)
7	62-66	101	mild	R-White Matter	56	57	57	*1 (1)
8	40-44	2645	severe	R-Frontal Parietal	7	7	7	0 (0)
9	55-59	588	severe	R-MCA	3	4	0	*1 (-3)
10	45-49	452	severe	L-Hemorrhagic Stroke	0	2	0	*2 (0)
11	30-34	494	mild	L-ICA	57	57	57	0 (0)
12	60-64	44	mild	L-PCA	57	57	57	0 (0)
13	57-61	849	mild	L-MCA	57	57	57	0 (0)
14	44-48	3017	severe	R-MCA/ R-FI	3	4	5	*1 (2)
15	69-73	790	severe	R-MCA/ R-TP	3	0	3	-3 (0)
16	78-82	631	mild	R-Occipital	57	57	57	0 (0)
17	75-79	5125	severe	R-MCA/ACA	9	11	10	*2 (1)
18	42-46	177	mild	L-MCA	57	57	57	0 (0)
19	62-66	392	severe	R-Frontal Hematoma	3	5	16	*2 (13)
20	55-59	2767	mild	R-VAOA, Subarachnoid Hemorrhage	57	57	57	0 (0)
21	69-73	783	severe	R-MCA	0	0	0	0 (0)
Mean	61.6	1127			26.6	27.9	28.9	1.3 (2.2)
(A) Median	61.9	588			9	11	16	0 (0)
SD	15	1327			26.4	26.6	25.9	3.9 (4.5)
Mean	61.1	1289			11.4	13.4	14.8	2 (3.4)
(B) Median	64	584			3	4	7	1 (1.5)
SD	13.5	1497			18	20.2	19.6	4.7 (5.2)

ARAT Indicates Action Research Arm Test; MCA Indicates Middle Cerebral Artery; ICA Indicates Internal Carotid Artery; PCA Indicates Posterior Cerebral Artery; FI Indicates Frontoparietal Infarct; TP Indicates Temporalfrontal-Parietal; ACA Indicates Anterior Cerebral Artery; MHR Indicates Motor Hand Region; VAOA Indicates Vertebral Artery Origin Aneurysm; L, Left; R, Right. ARAT Change: Completion-Baseline (FollowUp- Baseline). (A) Indicates descriptive statistics for all (n = 21) participants; (B) Indicates descriptive statistics for (n = 14) participants able to achieve ARAT improvements (ceilings removed).

Table 1: Participant Characteristic and ARAT score

Inclusion–Exclusion Criteria

Participants aged 18 years or older with persistent UE motor impairment resulting from stroke and no other known neurologic (cognitive, expressive), psychiatric (affect), or developmental disabilities were included. Exclusion criteria were; allergy to electrode gel, surgical tape, metals, concurrent treatment for infectious disease, apparent lesions or inflammation of the oral cavity, pregnancy or intention to become pregnant during the course of the study, or any contraindication for magnetic

resonance imaging (MRI). Subjects from the greater study cohort were excluded from the presented analyses if they (1) failed to complete at least 9 of 15, two-hour BCI intervention sessions occurring at least twice each week, (2) failed to complete all four MRI and behavioral testing sessions occurring in the intervention phase (Figure 1).

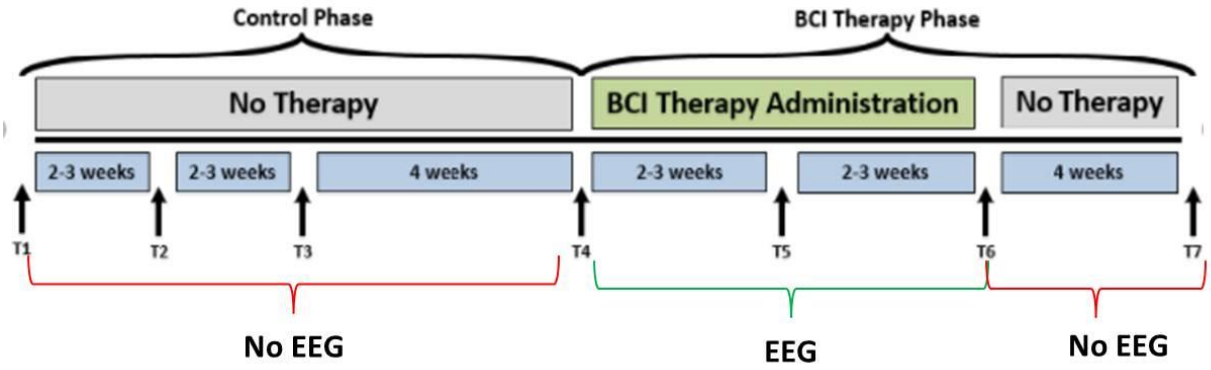


Figure 1: Study design. The time-points at which neuroimaging data were collected are represented by, T1: Control Baseline, T2: Control Middle, T3: Control Completion, T4: Intervention Baseline T5: Mid-intervention, T6: Completion of Intervention, and T7: One-month Post-Intervention. While the crossover control group (DTG) completed visits T1 through T7, the immediate therapy (ITG) group completed only visits T4 through T7. EEG-BCI-FES intervention is only administered during the BCI Therapy Phase (green), from baseline (T4) to completion (T6), and EEG recordings are neither acquired between T1 – T4, nor between T6 and T7 during which only MRI and behavioral testing batteries are administered. EEG data were only collected during the intervention phase.

Randomization and Study Schema

Participants, when assigned to the intervention phase, have at least 9 and up to 15 EEG-BCI-FES intervention sessions (two-to-three sessions/week) wherein they receive EEG-BCI- FES intervention lasting up to 2 h for a potential total dosing of 30 h of EEG-BCI-FES intervention. Along with the EEG-BCI-FES intervention sessions, subjects also receive fMRI and behavioral testing at four time points: prior to the first EEG-BCI-FES intervention session (baseline), after the first few weeks of intervention (midpoint), following the final intervention session (endpoint), and again 1 month after the endpoint

assessment (follow-up). Subjects assigned to the delayed intervention group (DTG) are encouraged to continue with their normal and customary care while in the delay period. While in the delay period, participant EEG data are not recorded, and participants are instructed not to use a BCI device. During this time, there are three assessment visits consisting of MRI and behavioral testing which are matched in sequence and duration to those conducted in the BCI intervention period as demonstrated in Figure 1. After completion of the delay period, these participants cross over into the intervention phase and are assessed in accordance with previously described methods. All data and time points analyzed and presented herein were recorded during the BCI intervention period only, for all participants. EEG data were only collected during the intervention phase.

The BCI System

The BCI system and intervention sequence were consistent with those previously described (Wilson et al., 2012) (Song et al., 2014c) (Remsik et al., 2019) using BCI2000 software version 2 with in-house modifications for input from a 16-channel EEG cap and amplifier (Guger Technologies) and integration with the ball and target gaming visual display as well as tongue stimulation (TDU 01.30 Wicab Inc. (Kaczmarek, 2011)) and functional electrical stimulation (FES) (LG-7500, LGMedSupply; Arduino 1.0.4). FES of the UE was delivered through a pair of 2” × 2” square electrodes, commercially available stimulus isolator units, which ensure clean, opto- electrical isolation, placed securely on the affected forearm using highly conductive Electrolyte Spray and produced by the LG- 7500 Digital Muscle Stimulator LGMedSupply, Cherry Hill, NJ, United States). The electrodes were placed to facilitate either a grasping motion (finger flexion), or finger extension according to participant preference. Specific placement sites were superficial to flexor digitorum superficialis to facilitate hand and finger flexion, or superficial to extensor digitorum communis to facilitate hand and finger extension. The natural absence of a flexor digitorum superficialis tendon to the fifth digit in some individuals was not considered in this study design. Stimulation was controlled through the PC using an Arduino Uno R3 (Adafruit Industries, New York, NY, United States) and a simple Reed-Relay circuit, with the amplitude set to elicit observable muscle activation (e.g., finger grasping) without pain. The pulse rate of the stimulation was set

to 60 Hz in order to produce tetanic contraction of the muscle and the pulse width was set to 150 μs. The input signal, initially set to zero, was adjusted by steps of 0.5 mA, unless the stimulation became uncomfortable for the subject. The device was never set to deliver an output greater than 5 mA. In previous publications, the TDU (Kaczmarek, 2011) has been described and its use in a BCI paradigm detailed (Wilson et al., 2012). This BCI system uses the same TDU stimulation parameters as were reported previously (Wilson et al., 2012).

Brief Overview of the Procedure (EEG Tasks)

EEG-BCI-FES Intervention

Subjects went through intervention sessions on separate days. The number of EEG-BCI-FES intervention sessions varied across subjects with a mean of 13.8 ± 1.3. Each EEG-BCI-FES intervention session consisted of multiple runs of the 'Cursor Task' (mean of 31.3 10.5 runs per session), about 1/3rd of which included only visual feedback, and roughly two thirds of which were comprised of BCI facilitated functional electric stimulation of the impaired hand and lingual electrotactile stimulation through a tongue display unit (TDU) (Kaczmarek, 2011) (Wilson et al., 2012) (Figure 2). The EEG-BCI-FES device was driven by spectral power recordings from contralateral (to the hand active in the grasping task) EEG electrodes during cued attempted grasping movements of the hand which was designed to modulate the horizontal movement of a cursor (Schalk et al., 2008) in a computer display space as well as facilitate concurrent functional electrical stimulation of the participant's impaired UE (should the target appear on the side corresponding to their stroke-impaired hand). BCI classifier inputs were therefore at C3 and C4, respectively in Mu (8–12Hz) and Beta (18–26Hz) frequency bands in this design. Each EEG-BCI-FES (closed- loop) intervention session was preceded by an open-loop pre- therapy screening phase and followed by an open-loop post- therapy screening phase (Figure 2). The successive order of intervention procedure was as follows: visual only, visual FES, visual and FES and electrotactile tongue feedback. All intervention sessions included in this analysis contained a similar distribution of these conditions across all participants.

Familiarization With BCI Device and Procedures

The first BCI session was focused on assisting the participant to comprehend and engage the BCI device and protocol. Stroke survivors often present with a myriad of cognitive, affective, and physical impairments (Nair et al., 2015) and out of respect for individual participant needs and abilities, the researchers intended to provide at outset an opportunity for a generous orientation rather than rigorous acquisition. During this preliminary session, the EEG cap (Figure 3), FES device, and TDU device were faithfully administered as described previously (Wilson et al., 2012). Participants were verbally instructed before each session, and as needed, to aim for successful completion of BCI tasks and for each attempted movement to be performed to the participant's autonomously elected level of comfort and ability. There were no participants in this study who were unable to comprehend or participate successfully in the intervention protocol as a result of any associated cognitive or aphasic impairments associated with their stroke. The study design requires at least 10 runs for each closed-loop condition, per session; however, enforcement discretion was encouraged until a participant demonstrated task comprehension during the first BCI intervention session.

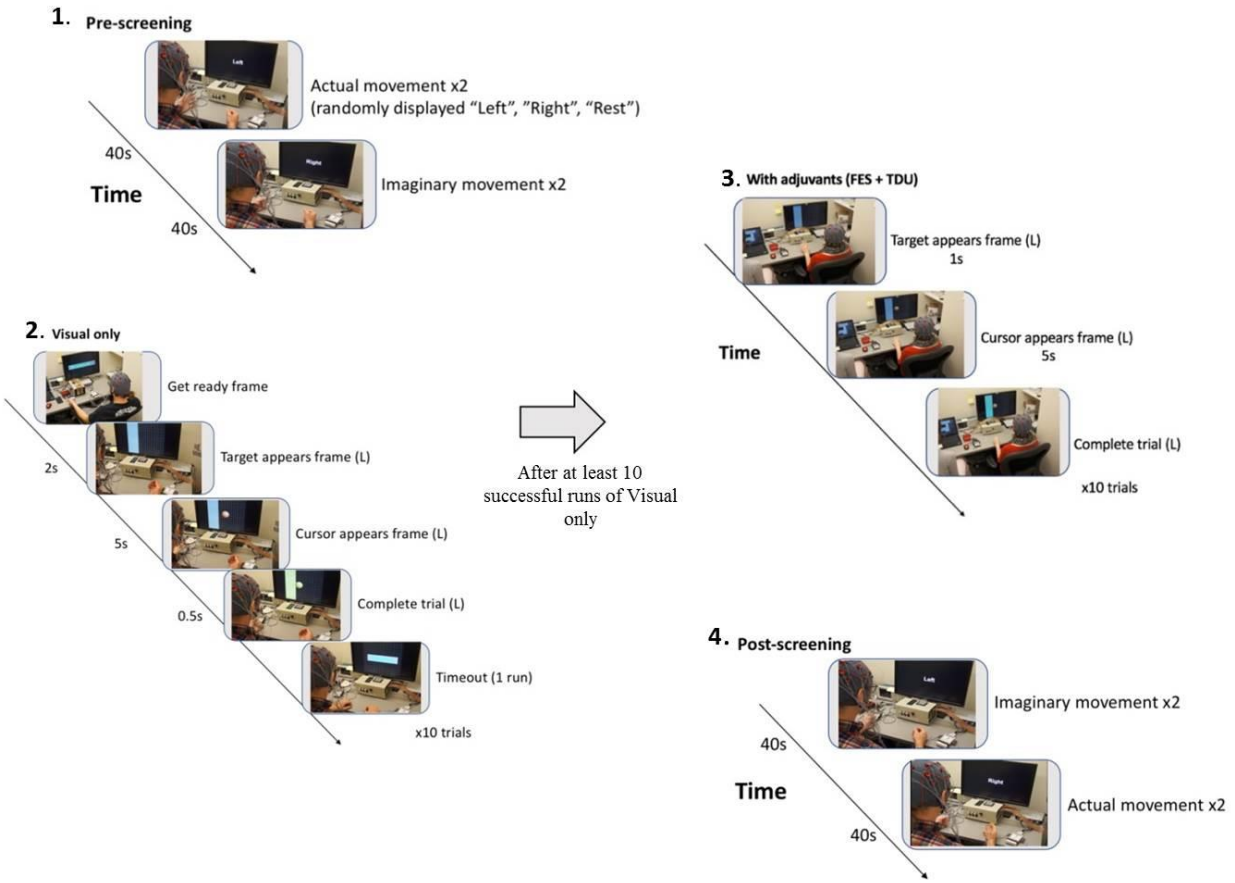


Figure 2: BCI intervention block design: 1.) Pre-secreening (two actual movement trials, two imagined movement trials), **2.)** Cursor task (≥10 trials with visual-only feedback), **3.)** Cursor task with adjuvant stimuli (≥10 trials with adjuvant stimuli), **4**.) Post-screening (two imagined movement trials, two actual movement trials).

Description of the Raw EEG Data

EEG data were recorded using a 16-ch bioamplifier (g.USBamp; G.TEC Medical Engineering GmbH, Austria) from 16 active electrodes using a g.GAMMA cap (F5, C5, FC1, C3, P5, F6, C6, P6, Pz, P4, P3, FC2, Cz, CP2, C4, CP1) (Figure 3) according to 10-20 EEG electrode placement system with a right ear-lobe reference in a BCI2000 system environment (Schalk et al., 2004). The frequency bandwidth of the recorded signals was 0.1–100 Hz, with an additional notch-filter applied at 60 Hz. The sampling rate was 256 Hz. During each of the screening phases (pre- and post-therapy) EEG data were collected in four separate runs. Each screening EEG data file contained 15 trials for rest, left hand and right hand

movements (i.e., five trials for each of the three conditions), separated by an interstimulus interval of 1.5–2 s. The order of trials in a run was random. Each of the trials had a duration of 4 s. The first two runs of the pre-therapy screening phase and the last two runs of the post-therapy screening phase incorporated cued "attempted" hand movements. The last two runs of the pre-therapy screening phase and the first two runs of the post-therapy screening phase incorporated cued "imaginary" hand movements.

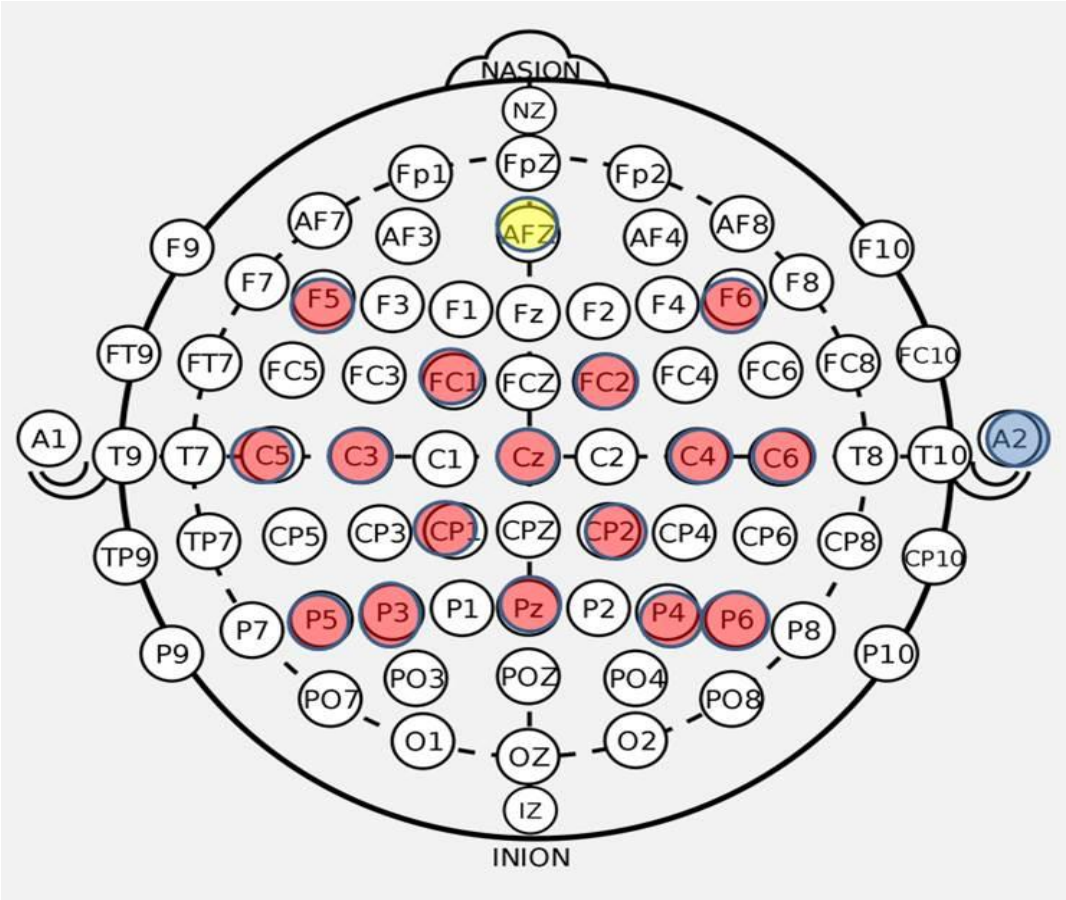


Figure 3: BCI Cap Array: Electrode array and cap arrangement for all n=21 participants. Control signals generated at C3 and C4 electrodes for right and left hand movement trials respectively. Ear clip always placed on the right ear.

Description of the EEG Data Analysis

The raw EEG data files were loaded into Fieldtrip (a MATLAB- based toolbox for advanced neurophysiological data analyses), and fully processed using tools incorporated in this toolbox (Oostenveld et al., 2011) and MATLAB environment (https://www.mathworks.com/). The main

processing steps for the EEG data collected during screening phases were as follows: (1) Digital filtering with a high-pass filter cutoff of 4 Hz, and a low-pass filter cutoff of 30 Hz. (2) Extraction and grouping of trials according to condition (rest, left hand movement, right hand movement), movement type (attempted, imaginary), and the screening phase (pre, post). This resulted in 10 trials for each of condition/movement/screening phase combinations. (3) Identification (variance based: thresholds set to 10 and 250 µV2 for low and high variance signals, respectively) and repair of bad (noisy) channels (spline interpolation), followed by the removal of three trials showing the highest variance (Thomson, 1982) (Mitra and Pesaran, 1999). The channel was identified as bad (noisy, poor connection, etc.) if the variance was <10 or >250 µV2 in more than three trials (Thomson, 1982) (Mitra and Pesaran, 1999). The units of the variance were those of the data squared: as the EEG data units were in micro-Volts, the variance units were squared micro-Volts. If more than four channels were identified as bad, the data for that session were removed from further analysis (i.e., 20.4% of data were discarded by not meeting the defined criteria). At session level, this step resulted in 28 s of EEG data (7 trials x 4 s) for each condition/movement/screening phase combination set. (4) An average-reference montage was applied to the data (i.e., re- referencing from the original monopolar recordings). (5) Spectral analyses with Fourier transforms computed using a multi-taper method (Thomson, 1982) (Mitra and Pesaran, 1999) at a 0.25 Hz resolution: this finally resulted in estimates of absolute spectral power sampled for every 1 Hz bin during the interval of 4–30 Hz, and cross-spectral density. The trial length was 4 s and the resolution of Fourier Transforms was 1/4 = 0.25 Hz. (6) Coherence estimation was calculated between all pairs of channels (120 pairs from 16 available scalp channels) at every 1 Hz frequency bin of the mentioned interval. Coherence was calculated as the absolute value of the ratio of the cross-spectrum to the square-root of the product of the two auto-spectra (as applied in Fieldtrip software). (7) Calculation of signed r-squared (r-squared: coefficient of determination) values from the absolute power estimates between left or right hand movements and rest trials, and between the two movement conditions (left vs. right). The r-squared values were signed in a such way that a large negative number (-) would mean larger “desynchronization” of the rhythm (Mu or Beta) (Pfurtscheller et al., 1997) (Neuper and Pfurtscheller, 2001) (Pineda, 2005). (8)

Calculation of change (POST–PRE) in signed r-squared values: the following formula was used: (POST–PRE), so one would obtain positive numbers for "increases" in desynchronization. This was done for easier interpretation of the associations of r-squared changes with behavior changes as the result of EEG-BCI-FES intervention. Here the "flipping" of values (in order to assess the "impaired hand," L or R) was applied to the impaired R-hand scores to put them together with scores from the impaired L-hand subjects. (9) Calculation of the laterality index (LI) for averaged coherence values (i.e., average coherence of each site with all others), used to evaluate shifts in coherence, as: (C3 - C4)/(C3 + C4). (10) Change (POST–PRE) in coherence LI values: LI as a number becomes more positive if there is a shift toward Left, and more negative if there is a shift toward Right (as the result of intervention). Therefore, for POST–PRE change in LI, the impaired L-hand values were multiplied with (-1) and the impaired R-hand values remained unchanged, as they were originally calculated. This way, the "expected change" is positive and the associations with behavioral changes can be more easily interpreted.

Statistics

The independent variables were the signed r-squared values and the coherence estimates. At individual subject level, the data consisted of average estimates per each session for condition/movement/screening phase combination sets, and at group level the estimates consisted of grand averages over sessions of each individual subject data in the group (pre- and post-therapy scores averaged separately across sessions). Non-parametric statistical tests were run by calculating Monte-Carlo estimates of the significance probabilities and critical values from the permutation distribution (Maris and Oostenveld, 2007; Maris et al., 2007), followed by correction for multiple comparisons using false discovery rate (FDR) when no prior hypothesis was available. The priori hypotheses of expected changes in the r-squared values and coherence as the result of intervention time at C3 and C4 sites were tested using paired t-tests in MATLAB. Associations between the r-squared changes and the total number of intervention runs as well as behavioral changes (e.g., ARAT scores) were assessed using Pearson's and Spearman's correlation, respectively. Finally, the associations between the signed r-squared values with behavioral scores from several tests at baseline were assessed using Spearman's or Pearson's correlation

coefficients, as appropriate. Thresholds for significance and trend toward significance were set a priori at $p \leq 0.05$ and $0.05 < p < 0.1$, respectively, for all statistical analyses.

Description of the Behavioral Outcome Measures

The primary outcome measure was the ARAT. The ARAT is a 57-point test designed to assess specific changes in upper limb function with sub-components for grasp, grip, pinch, and gross motor movement (Hsieh et al., 1998). The secondary measures include: The Stroke-Impact Scale (SIS), widely used to measure quality of life in stroke survivors that consists of 8 dimensions and a composite disability score (Vellone et al., 2015). The SIS is a 59- item patient-reported outcome measure, covering eight domains; strength (4 items), hand function (5 items), mobility (9 items), ADLs (10 items), memory (7 items), communication (7 items), emotion (9 items), and handicap (8 items); the domains are scored on a metric of 0–100, with higher scores indicating better self-reported health (Vellone et al., 2015). The National Institutes of Health Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify impairments caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between zero and four with higher scores indicating increased impairment. The Barthel scale, or Barthel ADL index, is a scale used to measure performance in ADLs (Shah et al., 1989b; a). It utilizes ten variables describing ADL and mobility. The ten variables addressed in the Barthel scale are: presence or absence of fecal incontinence, presence or absence of urinary incontinence, help needed with grooming, help needed with toilet use, help needed with feeding, help needed with transfers (e.g., from chair to bed), help needed with walking, help needed with dressing, help needed with climbing stairs, help needed with bathing. This scale yields a score of 0–100 with higher scores indicating improved performance (Shah et al., 1989b). Gross grasp grip strength was measured using a dynamometer (Nam et al., 2011). The Nine- Hole Peg Test (9-HPT) is a brief, standardized, quantitative test of UE function (Mathiowetz et al., 1985). The score for the 9-HPT is an average of the two trials (Mathiowetz et al., 1985). Mini- Mental State Examination (MMSE) is scored out of 30 (Pangman et al., 2000). An MMSE score of 27–30 is generally associated with normal memory: a score 10–26 could indicate mild to moderate dementia, and a score less than 10 suggests severe dementia (Pangman et al., 2000). The Center

for Epidemiologic Studies- Depression (CES-D) scale is one of the most frequently used self- report measures of depressive experiences (Shinar et al., 1986). The CES-D contains 20 items that are summed so that scores have a potential range from 0 to 60, with higher scores indicating greater frequency of depressive experiences (Shinar et al., 1986).

Analyses of Outcome Measures

Primary analysis was a paired-sample *t*-test to evaluate the statistical significance of ARAT and secondary outcome measure changes (i.e., SIS, NIHSS, Barthel scale, grip strength, 9-HPT, MMSE, and CES-D) between baseline, completion, and follow-up scores (Table 2).

Outcome Measures	Baseline Score	Completion Score	FollowUp Score	Change Score	*p* value
Stroke Impact Scale (SIS) (Max=100)					
$SIS_{Hand\ Function}$	33.6 (15) ± 38.1	39 (25) ± 37.5	39.8 (25) ± 39.7	5.4 (6.2)	0.482 *(0.050)
$SIS_{Recovery}$	50.1 (50) ± 23.7	53.4 (60) ± 24.9	54.6 (60) ± 21.8	3.3 (4.5)	0.509 (0.216)
NIH Stroke Scale/Score (NIHSS) (Max=4)	3.8 (3) ± 3.5	3.8 (2.5) ± 3.1	3.7 (2.5) ± 3.1	0 (-0.1)	1.0 (0.749)
Barthel Index-Total (Max=100)	91.4 (100) ± 14	92 (97) ± 13.9	92.8 (100) ± 14.8	0.6 (1.3)	0.431 (0.167)
Grip Strength (lbs)	18.8 (8.3) ± 21.5	22.6 (14.3) ± 23.5	20.5 (5) ± 24.6	3.8 (1.7)	*0.046 (0.246)
9-HPT (seconds)	17.7 (0) ± 22.8	15 (0) ± 19.1	14.4 (0) ± 20.3	-2.5 (-3.2)	0.083 (0.054)
MMSE (Max=30)	27.2 (29) ± 3.8	27.8 (29) ± 2.7	28.3 (29) ± 2.7	0.6 (1)	0.467 (0.494)
CES-D (Max=60)	7.6 (7.5) ± 5.8	7.8 (3) ± 9.9	5.6 (3) ± 5.9	0.2 (-2)	0.802 (0.096)
Action Research Arm Test (ARAT)					
$ARAT_{Total}$ (Max=57)	16.9 (9) ± 23	18.3 (11) ± 23.4	21.4 (16) ± 23.4	1.3 (4.3)	*0.046 *(0.020)
$ARAT_{Grasp}$ (Max=18)	2.2 (3) ± 5.1	2.9 (5) ± 5.3	3.6 (6) ± 6.3	0.7 (01.5)	0.106 (0.163)
$ARAT_{Grip}$ (Max=12)	2.9 (2) ± 4.7	2.9 (3) ± 4.8	3.8 (4) ± 4.6	0.1 (0.9)	0.582 *(0.025)
$ARAT_{Pinch}$ (Max=18)	4.5 (1) ± 7.3	4.9. (0) ± 7.9	5.1 (4) ± 7.7	0.4 (0.6)	0.289 (0.106)
$ARAT_{Gross}$ (Max=9)	3.4 (5) ± 2.7	3.4 (6) ± 3	3.6 (6) ± 3	0 (0.3)	1.000 (0.453)

Measures are reported as Mean (Median) ± SD. Change score & *p* value are reported as Mean scores change between Baseline and Completion (Mean scores change between Baseline and FollowUp). ARAT scores are reported as Mean scores change with ceilings removed.
* p < .05, **p < .01, ***p <.001

Table 2: Summary of mean outcome measure scores for Baseline, Completion, and Follow-Up of the BCI training conditions.

RESULTS

Results of Outcome Measures

Of the 21 participants who completed the study and met the aforementioned criteria, 14 participants had room for improvement in the primary outcome measure, ARAT ($ARAT_{total}$), of which nine (64%) realized improved scores after intervention, both at immediate completion and 1 month after completion. Participant characteristics are summarized in Table 1 and group outcome measures are further described in Table 2. All participant assessments at each time point were averaged to give a metric

of cohort motor function change at the group level. Secondary measures were similarly group averaged to determine cohort measure changes as a result of time in intervention as well as at the 1-month follow-up (Table 2). The primary analysis showed significant change in baseline scores and completion scores (Figure 1: T4, T6) in the primary outcome measure (ARAT) ($p = 0.046$) and change at follow-up ($p = 0.020$) (Figure 1: T7), change in Grip Strength was found to be significant by completion of intervention ($p = 0.046$). This particular finding did not persist at the 1-month follow-up time point. Statistical significance was observed in the baseline to follow-up score analyses (Figure 1: T4 to T7) not only for the primary outcome measure but also in secondary outcome measures of hand function (i.e., SIS Hand Function p = 0.05) (Table 2). All statistically significant findings were observed in measures of hand function. Additionally, the secondary analyses presented no significant results.

EEG Measures

Results reported below in Section "R-Squared" echoed in the graph in Figure 4, compared the signed r-squared values for the impaired hand separately from the non-impaired hand. The signed r-squared values from the Right-hand impaired participants at C3 (i.e., the ipsilesional motor site) were "pooled together" with the signed r-squared values from the Left- hand impaired participants at C4 (i.e., the ipsilesional motor site) consistent with methods described previously. Figures 4–8 display topoplots of group level averages of signed r-squared values and coherence values and do not use flipped-maps. Therefore, the maps for the left hand movements represent "an average" of these measures from impaired hand movements (as the majority of participants in this group were left-hand impaired) and non-impaired left hand movements (minority of subjects). In the same fashion, the maps for the right hand movements represent an average of these measures from impaired hand movements (minority of participants in this group were right-hand impaired) and non-impaired right hand movements (majority of subjects). In essence, the authors didn't flip the maps that are displayed in the figures.

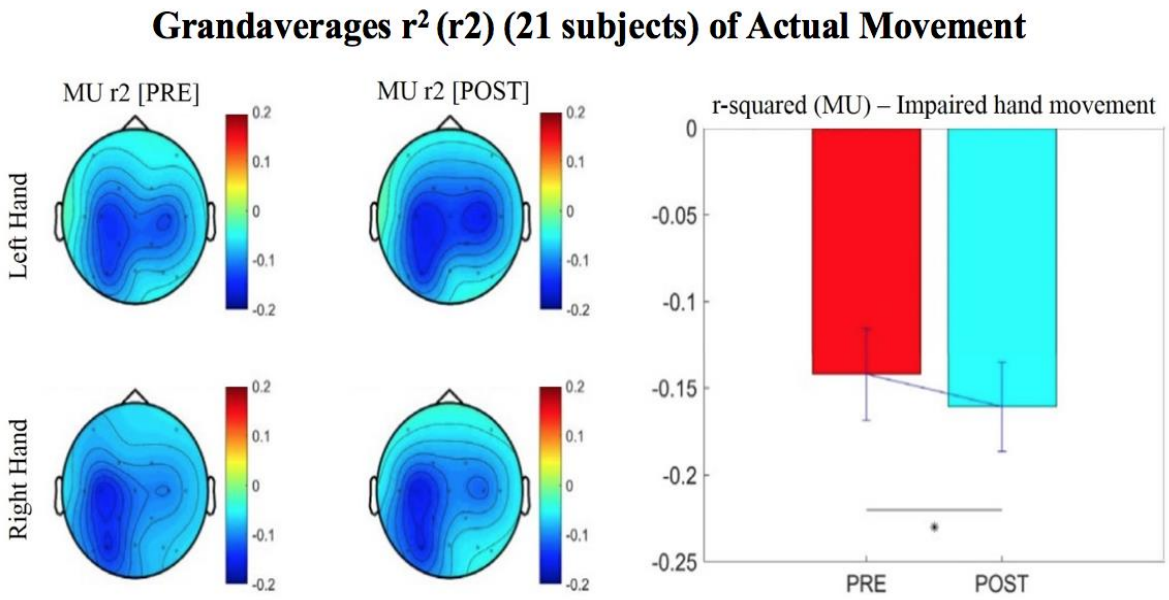


Figure 4: Topographical plots (topoplots) of grandaverages for Mu rhythm (8-12 Hz) signed r-squared values at group level (n=21). The bar plot shows the group means for the Mu rhythm signed r-squared values from the impaired hand attempted movement trials (vs rest) at ipsilesional electrode site. Asterisk denotes statistical significance from a one-tailed paired-t test ($p<0.05$). Error bars denote standard error of the mean. The majority of participants were left hand impaired. Prescreening, open-looped training (PRE) and open-looped postscreening BCI training (POST) runs (color bar: [-0.2 = blue – 0.2 = red]). The majority of participants had a right lateralized lesion.

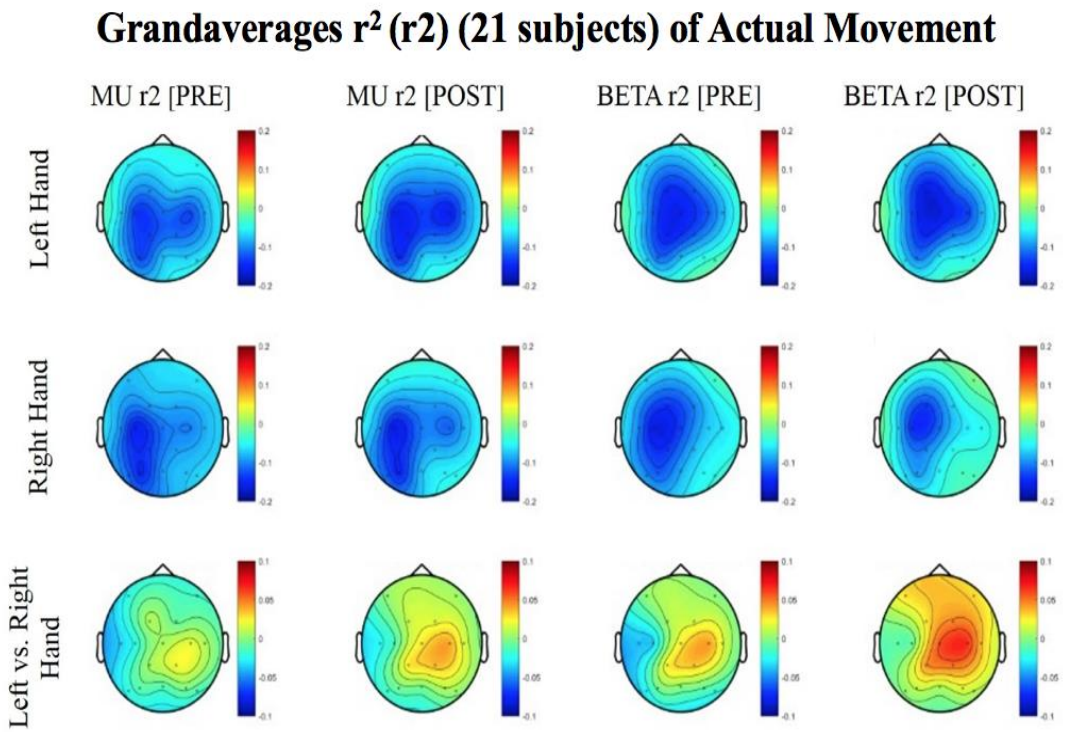


Figure 5: Topoplots of grandaverages for signed r-squared values at group level (n=21) for attempted movements. In the top two rows of topoplots, a larger negative value (blue) denotes stronger desynchronization (rest vs left or right hand actual movement); in the bottom row of topoplots a larger positive value (red) denotes desynchronization (left vs right hand actual movements). Note: The mentioned distinction reflects the way in which the signed r-squared values were calculated in a rest vs left/or right comparison, and in a left vs right comparison. Prescreening, open-looped training (PRE) and open-looped post screening BCI training (POST) runs (color bar: [-0.2 = blue – 0.2 = red]). The majority of participants had a right lateralized lesion. From

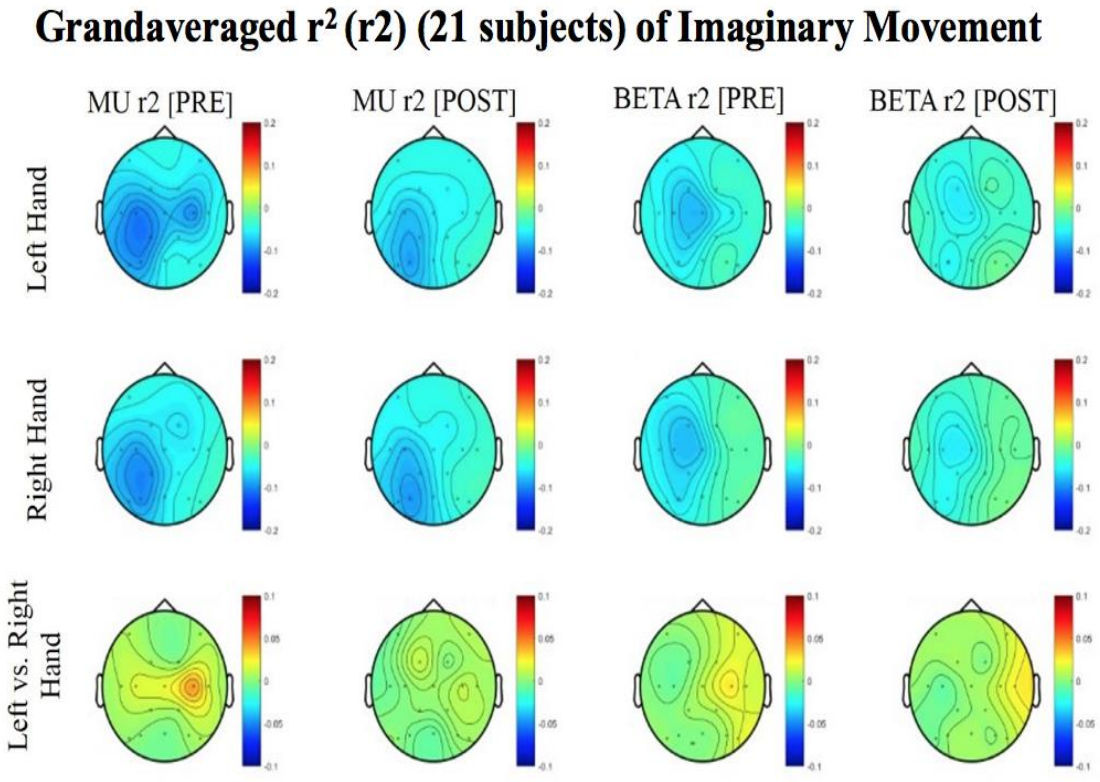


Figure 6: Topoplots of grandaveraged coherence values at group level (n=21) for Mu (8-12 Hz) and Beta (18-26 Hz) bands during attempted movement trials. Prescreening, open-looped training (PRE) and open-looped postscreening BCI training (POST) runs (color bar: [0=blue – 0.5=red]). The majority of participants had a right lateralized lesion.

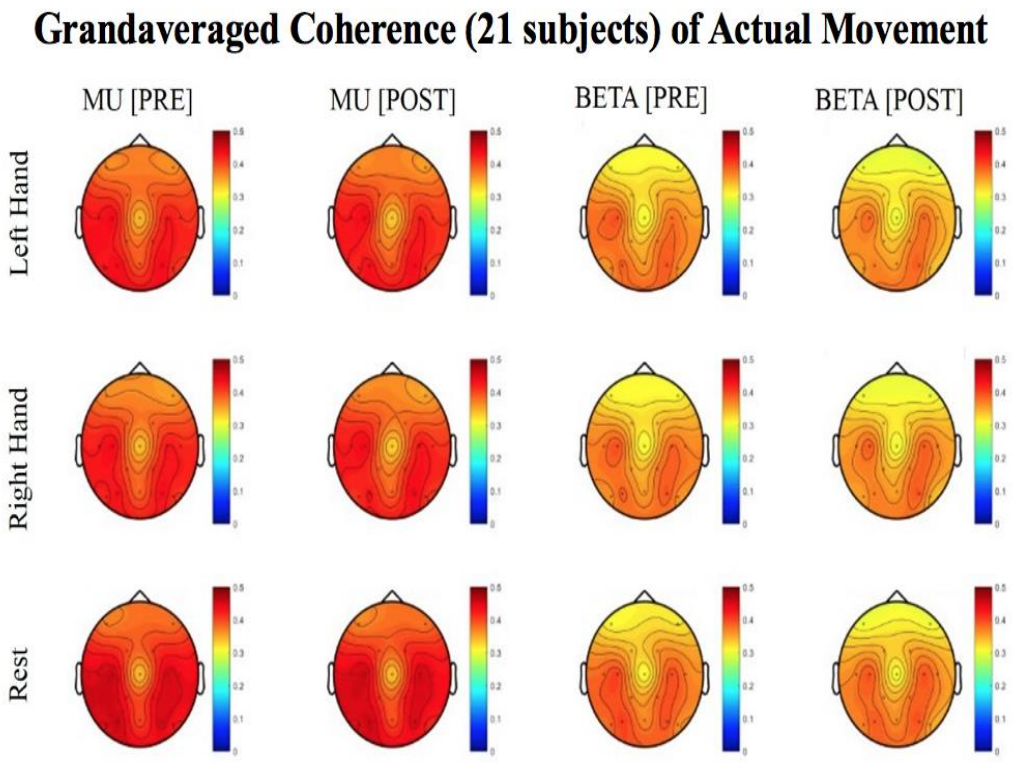


Figure 7: Topoplots of grandaverages for signed r-squared values at group level (n=21) for imaginary movements. Prescreening, open-looped training (PRE) and open-looped postscreening BCI training (POST) runs (color bar: [0 = blue – 0.5 = red]). The majority of participants had a right lateralized lesion.

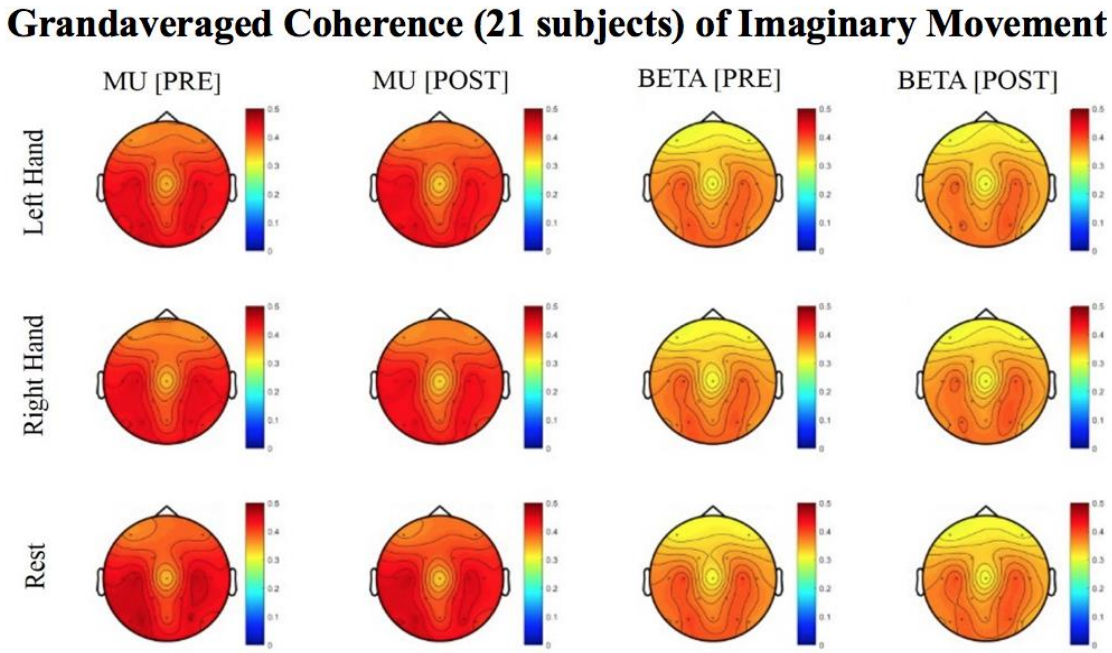


Figure 8: Topoplots of grandaveraged coherence values at group level (n=21) for Mu (8-12 Hz) and Beta (18-26 Hz) bands during imaginary movement trials. Prescreening, open-looped training (PRE) and open-looped postscreening BCI training (POST) runs (color bar: [0 = blue – 0.5 = red]). The majority of participants had a right lateralized lesion.

EEG Results

R-Squared

The signed r-squared value (at the ipsilesional C4 or C3 sites) for the Mu (8–12 Hz) rhythm significantly decreased in the post-therapy stage compared to the pre-therapy stage [one- tailed paired *t*-test: $t(20) = 1.85$; $p = 0.039$; meanPRE = -0.142; meanPOST = -0.161], while the subject attempted movements of the impaired hand (Figure 4). This suggests that as the result of the intervention sessions, the "desynchronization" of the Mu rhythm signals significantly increases post-therapy at the ipsilesional motor site. The bar graph displays the significant difference in the group mean r-squared values. The signed r-squared values of the Mu band signals decreased also post-therapy at the contralesional motor

site during attempted movements of the impaired hand, but these differences did not reach significance [one-tailed paired t-test: t(20) = 1.24; p = 0.114; meanPRE = -0.131; meanPOST = -0.145]. Figure 5 shows topographies of group-level grand averaged r-squared values obtained from data of 21 participants. Topoplots for both Mu and Beta bands are shown. While the presented results only describe changes in the Mu band, statistics from beta band did not reach significance. The Mu band and Beta band signals were both used for BCI control.

LI

Laterality index (LI) values, calculated from coherence estimates at C3 and C4 sites from Beta band (18–26 Hz) signals, decreased in post-therapy stage compared to the pre-therapy stage (one- tailed paired *t*-test: $t(20) = 0.983$, $p = 0.168$; meanPRE = 0.017; meanPOST = 0.009) while the subjects attempted movements of the impaired hand, although this change did not achieve statistical significance (Figure 6). This suggests that as a result of the intervention sessions, coherence in the affected motor site compared to the contralesional site showed a statistically insignificant increase at group level. Figure 6 shows topographies of group-level grand averaged coherence values from data of 21 participants. The value entered in each electrode site of the mentioned topographies represents the average coherence of that site with all others.

Imaginary Movement

Although no significant results were obtained from the analyses of data from imaginary movement trials, the topographical maps of r-squared and coherence values showed meaningful spatial distributions (Figures 7, 8). Figures 7, 8 show topographical maps (topoplots) of grand averages for signed r-squared values at group level (n = 21) and topoplots of grand averaged coherence values at group level for Mu (8–12 Hz) rhythm and Beta (18–26 Hz) band during imaginary movement trials, respectively. As the protocol was designed to train and reward attempted movements, it is possible participants were not sufficiently able to master imagined movement related SMR modulation.

Amount of Intervention: Number of Runs

The change in r-squared values (Beta band) in the ipsilesional hemisphere motor site during impaired hand attempted movements, following the intervention, showed a significant correlation with the total number of cursor trials (i.e., amount of BCI practice) runs [$r(20) = 0.393$; $p = 0.043$] (Figure 9). Item number eight in Section "Description of the EEG Data Analysis" clarifies that for the calculation of change (POST–PRE) in signed r-squared values the following formula was used: -(POST–PRE), so one would again obtain positive numbers for "increases" in desynchronization. This was done for easier interpretation of the associations of r-squared changes with behavior changes as the result of EEG- BCI-FES intervention and in accord with the previously described methods. In essence, the positive correlation suggests that a greater amount of BCI practice relates to "greater" ERD.

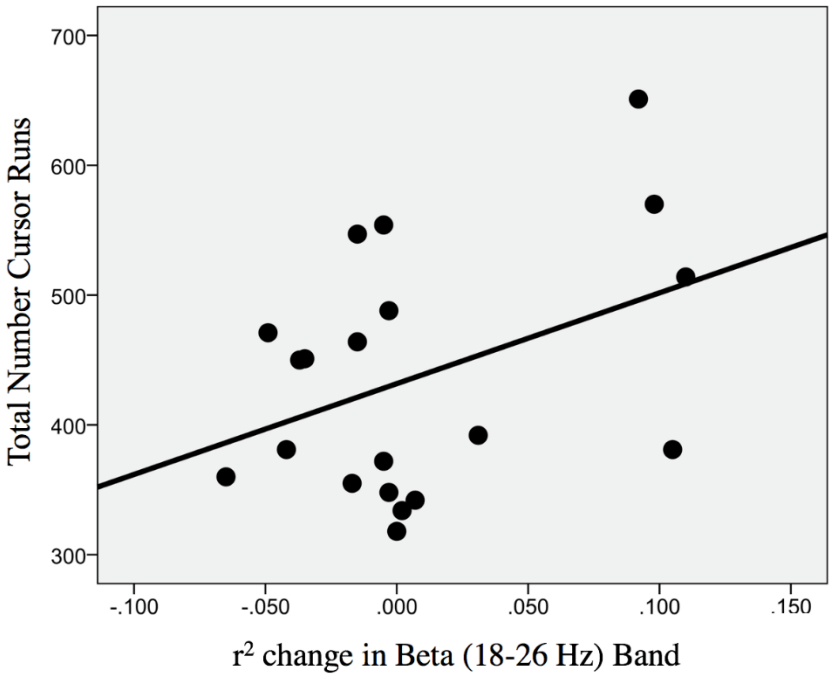


Figure 9: Association between the change in r-squared values (Beta band, 18-26 Hz) as the result of BCI training with the total number of cursor trial (i.e., intervention) runs (r(20) = 0.393; p = 0.043).

Influences on Primary Outcome Measure

In addition, the change in r-squared values (Mu rhythm) in the ipsilesional hemisphere motor site during impaired hand attempted movements, as the result of EEG-BCI- FES intervention, showed a

positive, non-statistically significant correlation with the change in ARAT scores (obtained post-therapy in comparison to baseline) [ρ(20) = 0.30; p = 0.098] (Figure 10).

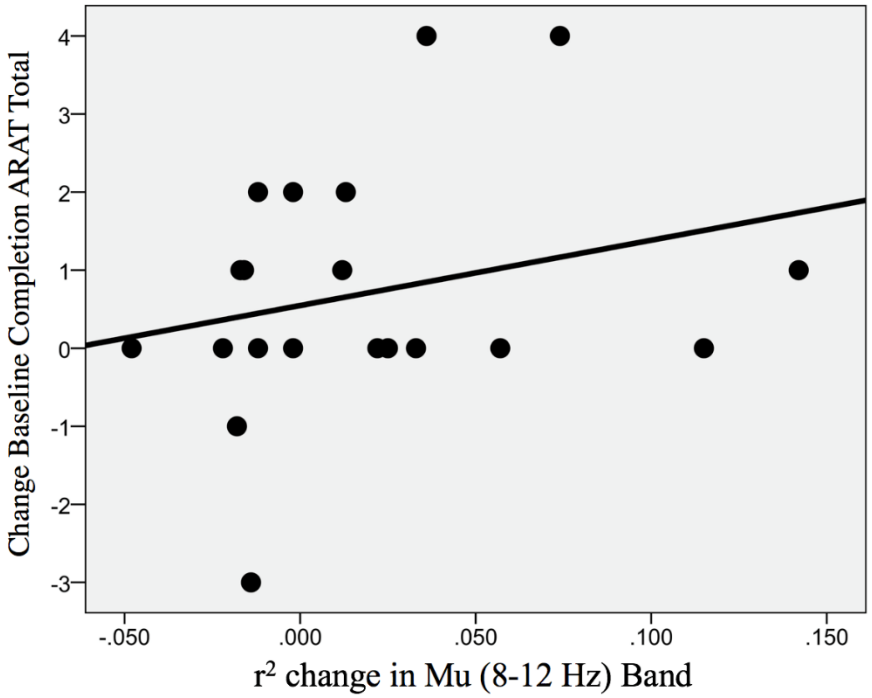


Figure 10: Association between the change in r-squared values (Mu rhythm, 8-12 Hz) as the result of BCI training with the change in ARAT scores (obtained post-intervention in comparison to baseline) (rho (20) = 0.30; p = 0.098).

Influences of Stroke and ERD on Baseline Behavioral Measures of Function and Capacity

Finally, to test some of the fundamental assumptions of the study design and BCI device (that diminished SMR desynchronization is related to the post-stroke impairment of simple motor outputs), signed Mu and Beta r-squared values for the impaired hand attempted at baseline (i.e., first intervention session) were compared to measures of behavior (SIS, ARAT, Grip Strength), and measures of stroke-related impairments to functional capacities (NIHSS, Barthel Index) at baseline (Table 3). A few measures of behavior (Grip Strength, SIS) and independence, capacity to perform ADLs (Barthel Index, NIHSS), correlated significantly in the anticipated direction (Table 3). Relevant statistical significance tests were chosen for normal and non-normal distributions, respectively. These results suggest that SMR

desynchronization may represent a fundamental neuromechanical component of motor capacity as well as motor learning and, therefore, any subsequent motor recovery potential.

Variables	Pre-screening MU	Pre-screening BETA
Baseline SIS Hand Function	rho=-0.449, p=0.041	rho=-0.408, p=0.066
Baseline SIS recovery	rho=-0.237, p=0.301	rho=-0.384, p=0.085
Baseline ARAT total	rho=-0.367, p=0.102	rho=-0.405, p=0.068
Baseline Barthel Index	rho=-0.292, p=0.199	rho=-0.573, p=0.007
Baseline Grip Strength	r=-0.369, p=0.10	r=-0.437, p=0.047
Baseline NIHSS	rho=0.244, p=0.28	rho=0.473, p=0.03

Note: Pearson's r was used for Grip Strength and Spearman's rho was used for all other variables (2-tailed tests).

Table 3:

Summary Pearson's r and Spearman's rho correlates of baseline outcome measures and EEG-based signed r-squared scores (*n*=21**)**

Adverse Events

No adverse events were reported during or after participation in the research experiment.

DISCUSSION

EEG Measure and Behavior Measure Fidelity

The findings that motor cortex EEG measures during attempted movements of the impaired hand (more specifically, r-squared values reflecting desynchronization levels of Mu rhythm and Beta band signals at key motor cortical sites) are positively correlated with behavioral changes and seem to offer a measurable link between electrophysiology and behavior is in line with the hypotheses set forth in this analysis. More importantly, the significant group level changes in r-squared values post-therapy compared to pre-therapy suggest an effect of the applied EEG- BCI-FES intervention protocol which may be beneficial for motor recovery, though data are currently inconclusive. As stated in Section “Amount of Intervention: Number of Runs,” the amount of BCI practice was positively correlated with Beta band

ERD of the ipsilesional motor cortex. Thus, it may be possible to conceive that, following adequate amounts of training; electrophysiological measures of connectivity such as coherence may allow additional insights into the potentials and mechanisms of functional change to the neuromuscular and neuromechanical coupling of effortful motor movement.

EEG Utility in Stroke Rehabilitation

A strength of this design and analyses for evaluation of objective physiological or functional changes as the result of the EEG-BCI- FES intervention is that the EEG-based measures extracted and compared were obtained immediately before, and immediately following each BCI intervention session (e.g., EEG-BCI-FES based rehabilitative intervention), at the pre and post screening periods (Figure 2). By comparing the EEG-based measure (i.e., r-squared, coherence) changes at post- to pre-intervention session, this allowed a more controlled evaluation of the specific effects of EEG-BCI-FES intervention. In addition, because the EEG signals are continuously recorded as part of the procedure, EEG-based measures can be obtained with no additional cost at any desired time (restricted only by the short interval required to extract reliable individual measure scores from spectral analyses of the signals). Furthermore, the study design allowed extraction and comparison of spectral estimates separately from attempted actual, as well as imaginary, hand movements. The current study did not, however, obtain statistically significant results when evaluating changes in EEG-based measures from imaginary hand movements at group level. This may be influenced by limited and insufficient time spent training participants to use imagination to properly control their SMR activity. Participants were explicitly and repeatedly instructed to attempt actual hand movements in an unblinded effort to regain or relearn volitional movement of their hands. None-the-less, reasonably distributed spatial maps of EEG activity in the SMR frequencies of interest from motor imagery attempts were observed (Figure 8). It is important, however, to note that motor imagery approaches are increasingly popular (Irimia et al., 2016) and might be a relevant means of EEG-BCI translation, particularly in stroke patients with severely impaired motor function.

Limitations

These results suggest that EEG-BCI-FES has the potential to induce neuroplastic change and aid recovery of UE paresis. However, this analysis was constrained by sample size and heterogeneity in lesion location, level of impairment, and time since stroke. Greater power is needed to adequately generalize these results. Utilizing a larger and more homogeneous subject cohort could allow for more generalizable conclusions in future research. Further, 16 electrodes were used in EEG signal data acquisition and EEG were recorded only during the intervention phase and at no other time during the study. While there is no EEG data recorded in the control period to compare with the recordings during intervention, there are brain (EEG) – behavior correlations specifically in EEG measures associated with motor function originating specifically from electrodes (C3/C4) (Figure 3) overlying regions conventionally attributed to motor function. Scalp or surface level EEG recordings are understood to read the dipolar or regional sources assumed to represent the synchronous activity of hundreds of thousands of underlying neighboring neurons. It is therefore possible that even if stroke lesions damage traditional cortical areas associated with motor output (primary motor cortex), perilesional brain regions, as well as established functional areas (pre-motor area and supplementary motor areas) may contribute to ipsilesional signal recordings sufficient to drive successful classifier activation (i.e., brain signal oscillations 'discrete' enough for the BCI to interpret SMR change and execute the relevant device or output command – in this case, horizontal cursor movement and facilitated FES activation) of a BCI.

Spatial Coverage and Sampling

It is generally understood that using 16 electrodes is insufficient for source localization, especially given the limited spatial coverage and non-equidistant spacing of the electrodes in this cap array (Figure 3) and thus, the present analysis does not consider such undertakings. In future research, the directionality and polarity of EEG-BCI-FES associated changes may lead to better understanding of the nature and sequence of motor related neuroplasticity as well as the neuroplastic influences of BCI technologies. Source reconstruction will be done once the sample size increases to sufficiently examine

this aspect in a subset of stroke participants with homogeneity in lesion location. Given the heterogeneity of lesion location in the existing sample set, source localization might be premature.

Statistical Approach

Such heterogeneity and restricted sample size similarly dissuaded the authors from attempting further conservative controls, such as multiple comparisons corrections. The authors conceived that further conservative data manipulations may wash out any potential ('trending to') significant relationships the authors or other groups may want to follow-up with future research. This manuscript, part of a larger on-going clinical trial, is an interim analysis which sought to elucidate any significant trends in the data as the study progressed so as to inform our future questioning of the data and to be better prepared to identify and test potentially significant interactions and factors in the larger post-stroke population.

Nature of the Academic Research Environment

This is an on-going study in its seventh year of data acquisition and participant enrollment. Various project personnel have undergone and supervised the staffing, training, and data acquisition of this trial during its course. The authors work hard to best minimize differences in acquisition of study measures through extensive and repeated training of personnel.

Future Scope

Despite the existing challenges to providing evidence-based treatment strategies in the stroke rehabilitation field, combined therapies may be used to achieve the maximal motor function recovery for participants (Oostenveld et al., 2011). Development of effective strategies for rehabilitation of impaired motor functions in stroke patients, as well as for monitoring and evaluation of changes during an applied intervention is yet needed.

CONCLUSION

EEG Conclusions

Non-invasive EEG-based measures of motor cortex function, such as r-squared (reflecting desynchronization levels of the relevant SMR rhythms), could provide an efficient means of tracking and even predicting functional changes in stroke patients during the course of the EEG-BCI-FES intervention.

As ERD changes were reported at the group level, and given the heterogeneity in the sample, it may be argued that the reported changes not only suggest a change in function for the majority of participants (despite few changes attaining clinically significant differences) but also, given more selective sampling and independent variable control, an even more clinically relevant relationship between ERD and recovery may exist. Tracking SMR modulations may be a potential predictor of recovery or indicator of recovery potential in a patient.

BCI Conclusions

The observed effects to motor measures might also be a consequence of challenging and rewarding movements associated with (ADLs), which the participants previously may have thought to be impossible or too difficult to produce successfully. BCI intervention may help challenge a survivor's individual conception of their limitations by pushing a participant to use the affected hand and rewarding them (according to an anticipatable, clear, and consistent schedule) for doing so. This is to suggest that the minimal gains observed by most participants, in comparison to the significant gains obtained by some, and their absence in others, may be related to the encouragement of attempting previously ineffective motor behaviors. It is possible the statistically significant gains observed, supported by the higher incidence of significance in subjective measures than the number of lab-based objective measures, could be the result of the specific reward structure of the design in addition to, or more so than any reliable neuromechanical or electrophysiological contributions.

Biological Limitations and Contribution of Learning Theories

If normal muscle synergies (e.g., the same muscles act to abduct one's arm each time, in a healthy adult) are disrupted by an insult such as stroke, robbing the motor circuity of its primary output components (e.g., central nervous system efference to peripheral nervous system effectors), residual functional capacities are limited by the ability of the system to retrain or re-map (link) the CNS commands to PNS effectors (Power et al., 2011). Successful BCI intervention must connect the peripheral muscle activation with the muscle effectors necessary to execute a motor function according to the user's CNS command to do so. Unfortunately, retraining the processes of the descending motor system is not

always an option as stroke often results in irreparable tissue damage or death to motor pathways and even their sensorimotor confederates. Post-stroke neuronal loss alters recruitment of downstream muscle synergies (Cheung et al., 2009), and alters a synergy's internal structure (Roh et al., 2013) depending on stroke severity (Roh et al., 2015). One biological mechanism left to these survivors is to adapt existing synergistic capacities toward a compensatory strategy (e.g., recruitment of novel synergistic families to accomplish a familiar movement). Thus, future BCI methodologies should rely on classical conditioning and Hebbian learning theories as well as predictive modeling for developmental guides to practice. Future BCI designs may also benefit from classification of distal muscle capacities and synergistic integrities so as to better measure, represent, facilitate, or compensate for the functional consequences of the stroke disturbed CNS and PNS circuitry.

From previously published findings (Young et al., 2014a) (Song et al., 2015b), we can comprehend that BCIs induce neuronal changes which, in turn, might help the participants challenge their paresis or perceived disabilities (Dromerick et al., 2009), as they access or develop (i.e., train) new functional aptitudes, or reinvigorate old synergies and neural networks dampened by insult (Remsik et al., 2016). Participants may have the perception that their ability has improved or changed; however, when assessed by objective measures, those perceptions, at least here, are not always confirmed at equal magnitude. The authors posit that neural changes reported by other groups and in our previous publications may not always manifest as clinically significant objective changes in motor function because there is either, or both a threshold effect, or a missing component to this type of intervention (such as sufficient dosing parameters, subject selection, etc.). This opinion is potentially fortified by these results which suggest more time in intervention is related to greater electrophysiological change. Electrophysiological changes are understood to be possible biological precursors to function network change and eventually, functional behavioral change. Other than the simple explanation that objective lab-based measures might not reliably capture UE impairment well in stroke survivors, perhaps, as a result of engaging with this BCI intervention, this discrepancy might also arise because participants are

beginning to engage their environment with the distal musculature of the impaired hand in ways they had been previously averse (unwilling) or unable to.

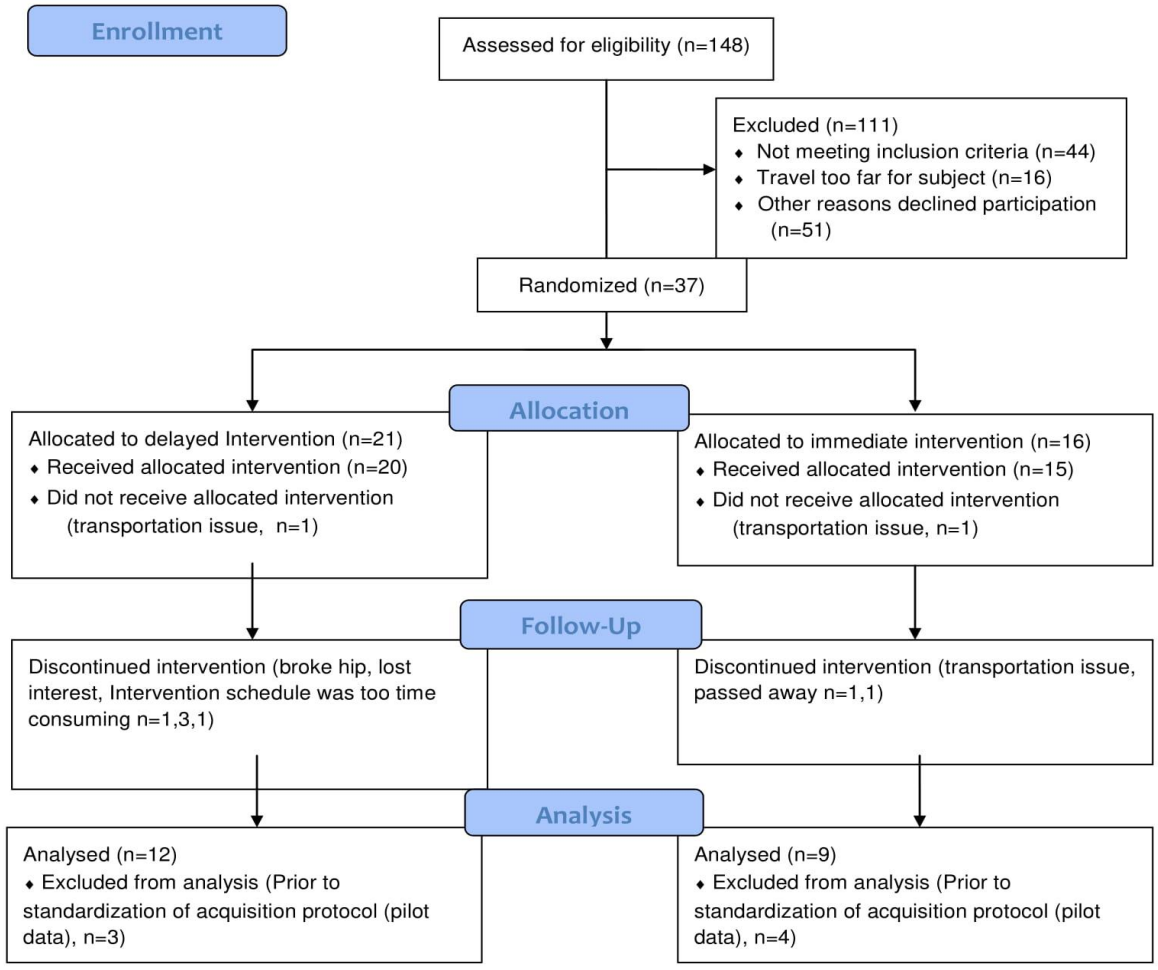
More Intervention

Losing strategies, more often than not, do not win (e.g., adaptive vs. maladaptive behaviors). Maladaptive associations may simply need more time to be pruned away and relevant adaptive associations strengthened by increased and more highly structured reinforcement. If one assumes such a threshold effect, the neural- remodeling realized in these participants may suggest that more intervention trials were needed to translate to clinically significant, not just relevant, changes in objective measures of function. Results suggest a relationship between more trials and greater outcome measure change, paralleling a concept associated with training, or learning a new motor skill: practice makes permanent. It may be that amount of intervention, or inadequate 'dosage' in this case, explains the weak translation of observed brain level changes into behavioral gains for this cohort. Little evidence has thus far been offered to suggest an optimal BCI regimen. Perhaps there is even an upper limit, or even some consequence of fatigue. It is therefore suggested that future research address these questions and aim to better understand dose-response relationships and independent variable (lesion location, lesion volume, time since stroke, comorbid impairments, etc.) contributions to predict recovery potential and more efficaciously prescribe BCI intervention as therapy. All BCI research would benefit by a concerted effort to identify a therapeutic index for various BCI interventions (regimens) as well as attempt to target ideal patient profiles for prescription of BCI intervention as a therapy.

Supplementary Materials**: CONSORT Flow Diagram**

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT Behavioral Flow Diagram



Chapter 5

Ipsilesional Mu Rhythm Desynchronization Correlates with Improvements in Affected Hand Grip Strength and Functional Connectivity in Sensorimotor Cortices Following BCI-FES Intervention for Upper Extremity in Stroke Survivors

Remsik AB, Gjini K, Williams L Jr, van Kan PLE, Gloe S, Bjorklund E, Rivera CA, Romero S, Young BM, Nair VA, Caldera KE, Williams JC and Prabhakaran V (2021) Ipsilesional Mu Rhythm Desynchronization Correlates With Improvements in Affected Hand Grip Strength and Functional Connectivity in Sensorimotor Cortices Following BCI-FES Intervention for Upper Extremity in Stroke Survivors. *Front. Hum. Neurosci.* 15:725645. doi: 10.3389/fnhum.2021.725645.

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ABSTRACT

Stroke is a leading cause of acquired long-term upper extremity motor disability. Current standard of care trajectories fail to deliver sufficient motor rehabilitation to stroke survivors. Recent research suggests that use of brain-computer interface (BCI) devices improves motor function in stroke survivors, regardless of stroke severity and chronicity, and may induce and/or facilitate neuroplastic changes associated with motor rehabilitation. The present sub analyses of ongoing crossover-controlled trial NCT02098265 examine first whether, during movements of the affected hand compared to rest, ipsilesional Mu rhythm desynchronization (ERD) of cerebral cortical sensorimotor areas (Brodmann's areas (BA) 1-7) is localized and tracks with changes in grip force strength. Secondly, we test the hypothesis that BCI intervention results in changes in frequency-specific directional flow of information transmission (direct path functional connectivity) in BA 1-7 by measuring changes in isolated effective coherence (iCoh) between cerebral cortical sensorimotor areas thought to relate to electrophysiological signatures of motor actions and motor learning. A sample of 16 stroke survivors with right hemisphere lesions (left hand motor impairment), received a maximum of 18–30 h of BCI intervention. Electroencephalograms were recorded during intervention sessions while outcome measures of motor function and capacity were assessed at baseline and completion of intervention. Greater desynchronization of Mu rhythm, during movements of the impaired hand compared to rest, were primarily localized to ipsilesional sensorimotor cortices (BA 1-7). In addition, increased Mu desynchronization in the ipsilesional primary motor cortex, Post vs. Pre BCI intervention, correlated significantly with improvements in hand function as assessed by grip force measurements. Moreover, the results show a significant change in the direction of causal information flow, as measured by iCoh, toward the ipsilesional motor (BA 4) and ipsilesional premotor cortices (BA 6) during BCI intervention. Significant iCoh increases from ipsilesional BA 4 to ipsilesional BA 6 were observed in both Mu [8-12 Hz] and Beta [18-26 Hz] frequency ranges. In summary, the present results are indicative of improvements in motor capacity and behavior, and they are consistent with the view that BCI intervention improves functional motor capacity of the ipsilesional hemisphere and the impaired hand.

INTRODUCTION

Stroke is a leading cause of acquired upper extremity (UE) motor disability and many survivors are left with persistent upper extremity motor impairments requiring rehabilitation (Benjamin et al., 2019) (Benjamin et al., 2019). In the United States alone, on average, every 40 seconds someone suffers a stroke (Benjamin et al., 2019). About six months after stroke insult, approximately half of stroke survivors continue to suffer residual motor deficit (Benjamin et al., 2019). Stroke burden on the United States economy, by 2050, is expected to be above $2.2 trillion (Benjamin et al., 2019). Despite advances in acute stroke care, the estimated direct and indirect costs of stroke continue to escalate and are disproportionately associated with long-term care and rehabilitation.

Electroencephalogram-based brain-computer interface (BCI) intervention has been proposed as a novel intervention tool (Pfurtscheller and Berghold, 1989) (Pfurtscheller et al., 1997) (Neuper and Pfurtscheller, 2001) (Wolpaw et al., 2002) (Leuthardt et al., 2004) (Schalk et al., 2004) (Pfurtscheller et al., 2005a) (Birbaumer et al., 2006) (Wilson et al., 2009a) (Prasad et al., 2010) (Schalk and Mellinger, 2010) (Bundy et al., 2012) (Babaiasl et al., 2016) (Irimia et al., 2016) (Young et al., 2016) (Mazrooyisebdani et al., 2018) (Mohanty et al., 2018) (Remsik et al., 2018) capable of enhancing motor recovery post-stroke. The neural mechanisms underlying BCI's effect on motor rehabilitation, either through neural plasticity or otherwise, are not well understood. BCIs are a promising supplement to existing means of neurorehabilitation but may also function as tools that provide insight into the sensorimotor processes underlying motor function and motor learning in either healthy or stroke-lesioned brains. Damage to the input (afferent) or output (efferent) pathways of the sensorimotor system creates a demand for reorganization of existing neural network functions (with respect to completion of behavioral goals) (Nudo, 2011) (Nudo and McNeal, 2013). BCIs may induce or facilitate neuroplasticity by strengthening such connections between brain areas (Song et al., 2014c) (Young et al., 2014a) (Song et al., 2015b) (Biasiucci et al., 2018).

EEG activity recorded from sensorimotor cortices (BA 1-7) of each hemisphere desynchronizes with imagined and attempted movements, and preparation of movement. This phenomenon is known as event-related desynchronization (ERD) (Pfurtscheller and Berghold, 1989) (Pfurtscheller, 1999) (Pfurtscheller and Lopes da Silva, 1999) (Neuper and Pfurtscheller, 2001) (Pfurtscheller et al., 2005a) (Pineda, 2005) (Neuper et al., 2006) (Nam et al., 2011). Specific frequency bands are associated with components of event-related motor behaviors (Pfurtscheller et al., 1997) (Neuper and Pfurtscheller, 2001) (Pineda, 2005) (Nam et al., 2011). When healthy individuals plan and execute purposeful movements, Mu rhythms of the contralateral sensorimotor cortices are desynchronized and attenuated (Pfurtscheller et al., 1997) and increased presence of Beta rhythm ERD is associated with motor command output and control (Pfurtscheller, 1999) (Pineda, 2005) (Nam et al., 2011). ERD and event related synchronicity (ERS) were key components in the use and development of early EEG-based BCI motor rehabilitations (Wolpaw et al., 1991) (McFarland et al., 2000) (Neuper and Pfurtscheller, 2001) (Wolpaw et al., 2002) (Leuthardt et al., 2004) (Schalk et al., 2004) (Neuper et al., 2006). Thus, ERD/ERS provide measures of volitional movement-related brain activity that can be decoded by a BCI to control a device, such as a prosthetic limb, or an output command, such as a cursor on a computer screen (Pfurtscheller et al., 1997) (Leuthardt et al., 2004) (Neuper et al., 2006) (Wilson et al., 2009a).

In human subjects, at frequencies around 10–20 Hz, Mu and Beta sensorimotor rhythms (SMRs) are recorded exclusively over cortical sensorimotor areas (BA 1-7) (Pfurtscheller et al., 1997) (Birbaumer and Cohen, 2007). Two basic strategies, motor imagery and attempted movement (Wolpaw et al., 1991) (Wolpaw et al., 2002) (Wilson et al., 2009a) (Nam et al., 2011) (Ortner et al., 2012) (Wilson et al., 2012) (Song et al., 2014a) (Irimia et al., 2016) (Remsik et al., 2016) as well as various therapeutic adjuvant approaches (e.g. BCI-FES) (Biasiucci et al., 2018) have been introduced for motor rehabilitation in stroke patients. Both approaches record SMRs as input signals (electrophysiological recordings by the EEG cap) to the BCI from overlapping neural architecture. This protocol was designed to utilize attempted hand movements during the intervention following the logic that a motor therapy designed to rehabilitate

volitional motor function of the affected UE should utilize voluntary attempted movements of an impaired hand in a continuous effort to improve the participant's UE capacity and performance.

The present sub analyses of ongoing crossover-controlled trial NCT02098265 examine first whether, during movements of the affected hand compared to rest, ipsilesional Mu rhythm desynchronization (ERD) (Pfurtscheller and Berghold, 1989) (Pfurtscheller et al., 1997) (Neuper and Pfurtscheller, 2001) (Pineda, 2005) (Nam et al., 2011) of cerebral cortical sensorimotor areas (Brodmann's areas (BA) 1-7) (Brodmann, 1909) is localized and tracks with changes in grip force strength. Secondly, we test the hypothesis that BCI intervention results in changes in frequency-specific directional flow of information transmission (direct path functional connectivity) in BA 1-7 by measuring changes in isolated effective coherence, iCoh (Pascual-Marqui et al., 2014) (Kitaura et al., 2017), between cerebral cortical sensorimotor areas thought to relate to electrophysiological signatures of motor actions and motor learning.

METHODS

Participant Population

Participants were recruited from the greater Madison, Wisconsin, United States area as part of an on-going cross-over controlled prospective randomized rehabilitation study investigating interventional BCI in upper extremity (UE) motor function impairment resulting from stroke. This study is approved by the University of Wisconsin Health Sciences Institutional Review Board (Study ID 20150469). All subjects provided informed written consent upon enrollment.

Study Design and Procedures

The BCI system and intervention procedures were consistent with previously published works, (Wilson et al., 2009a) (Wilson et al., 2012) (Song et al., 2014c) using BCI2000 software (Schalk et al., 2004) version 2 with in-house modifications for input from a 16-channel EEG cap and amplifier (Guger Technologies) and integration with a ball and target gaming visual display (Wilson et al., 2009a) and functional electrical stimulation (FES) adjuvant (Popovic et al., 2009) (Takahashi et al., 2012) (Biasiucci et al., 2018). A more detailed and complete description of the session and run procedures used in data

acquisition and analysis reported in this manuscript, as well as a description of the functional electrical stimulation protocol and justification for how this approach further improves the effects of BCI have been published previously (Remsik et al., 2019).

Sixteen right hemisphere stroke survivors (8 female, age = 62.5+12.7 years [mean+SD]) (Table 1) participated in 9-15 sessions (13.9+1.28 [mean+SD]; following removal of artifact EEG data: 11.1+3.87 [mean+SD]) with the BCI. Participants executed hand movements in response to visual cues displayed on a computer screen concordantly with corresponding audio instructions (e.g., Left, Right, Rest). One session (or run) of the cursor and target task consisted of 10 trials, or attempts, during which the participant attempted to drive a virtual cursor across the display screen into the target space using voluntary modulation of their sensorimotor rhythms (i.e. satisfaction of BCI classifier) before the trial timed out. BCI performance was measured as the number of successful trials (i.e. hits compared to misses) "out of a possible 10" attempts in any one run. This metric in included in Table 1 as “Average BCI Performance.”

Participant	Lesion Location	Time Since Stroke (days)	Age Range	Sex	Total BCI Runs	Average BCI Performance	ARAT Baseline	ARAT Change	Hand Grip Strength (lb) Baseline	Hand Grip Change (lb)
1	L. Lateral Medulla	160	45-49	M	502	6.094	3	-1	0	0
2	R. MCA	490	50-54	M	651	7.043	3	1	23.33	-10
3	Leg/periventricular white, MHR	658	75-79	M	488	5.76	57	0	51	-3
4	R-PLIC putamen	2,723	65-69	M	381	5.83	23	17	8.33	15.33
5	R. prefrontal, midfrontal, temporal	197	70-74	F	318	5.23	0	0	0	0
6	R. White matter	94	60-64	F	514	4.65	56	1	22.33	10
7	R. frontal parietal	2,645	40-44	F	464	4.9	7	0	1.33	5
8	R. Frontal-temporal-occipital	588	55-59	F	471	5.47	3	1	17	8.67
9	R. Anterior Temporal lobe; fronto-parietal regions	452	45-49	M	372	5.49	0	2	0	0
10	R. MCA/R. Frontoparietal infarct	3,017	45-49	F	392	6.92	3	1	0	0
11	R. MCA/R. Temporalfrontal-parietal	790	70-74	F	360	7.92	3	-3	0	0
12	R occipital	631	80-84	M	451	5.84	57	0	6.33	8
13	R. MCA/ACA	5,115	75-79	M	570	5.52	9	2	0	0
14	R frontal lobe// R frontal hemorrhagic infarct	392	60-64	F	381	5.83	3	2	0	0.33
15	R VAOA, subarachnoid hemorrhage	2,767	55-59	F	334	5.83	57	0	49	-7.33
16	R. MCA,	783	70-74	M	355	5.18	0	0	0	0
Mean		1343			437.75	5.85	17.75	1.44	11.17	1.69
SD		1449.64			92.47	0.84	23.88	4.34	17.22	6.41

Table 1: Demographics of n = 16 stroke survivors. One session (or run) of the cursor and target task consisted of 10 trials, or attempts, during which the participant attempted to drive a virtual cursor across the display screen into the target space using voluntary modulation of their sensorimotor rhythms (i.e. satisfaction of BCI classifier). BCI performance was measured as the number of successful trials (i.e. hits compared to misses) "out of a possible 10" attempts in any one run. Action Research Arm Test (ARAT) scores affected (i.e., left) hand motor impairment on a scale of 0-57; 57 indicating no measurable upper extremity motor impairment. Hand Grip Strength measured by dynamometer in pounds (lb.) of maximal whole hand grasp.

The BCI classifier was defined in 'screening' sessions (Pre and Post BCI intervention). Screening sessions contained two runs, each consisting of 15 trials for rest, left-hand, and right-hand movements (i.e., 5 trials for each of the three conditions, the order of trials in a run was random). Only the rest and left-hand movement trials are considered here.

From the larger NCT02098265 cohort, only participants with left hand motor impairment were selected for these sub analyses in an effort to control for homogeneity of stroke-related upper extremity impairment, and language or communicative deficits that might interfere with comprehension of the BCI task requirements or task execution.

Preprocessing of the Scalp EEG Data

Various EEG-signal processing techniques were used to estimate and further evaluate the spectral perturbations recorded over the course of BCI intervention. EEG data analysis and statistics were consistent with methods detailed previously (Remsik et al., 2019).

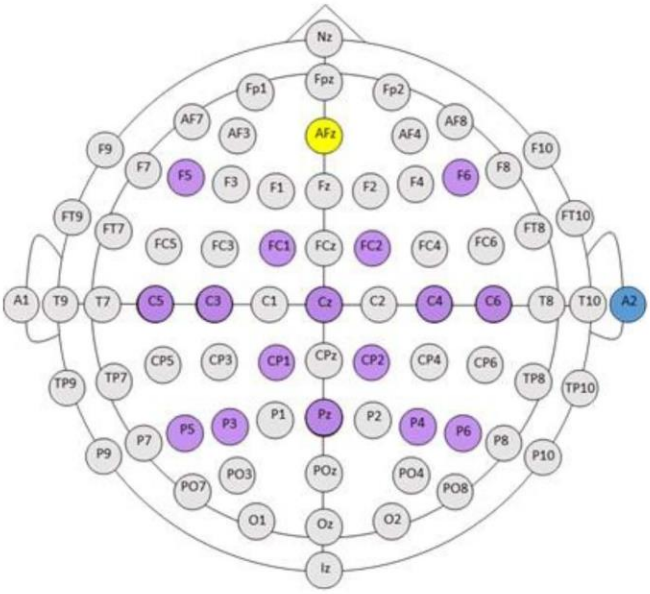

Figure 1: BCI cap array. International 10-20 system for standardized EEG electrode locations on the head: C = central, P = parietal, T = temporal, F = frontal, Fp = pre-frontal, O = occipital. Electrode array and cap arrangement for all n = 16 participants is indicated in purple against the standard 10-20 electrode array head map. AFz (yellow) is the ground electrode. A2 (blue) electrode is the reference electrode, placed on the back of the right ear. Please note, electrode arrangement is designed for increased density around cortical sensorimotor areas.

EEG electrodes were positioned according to the standard 10-20 system, grounded to Fpz, and referenced to an ear electrode placed on the back of the participant's right ear. Electrodes in the cap arrangement are highlight in purple in Figure 1 and contain electrodes F5, F6, FC1, FC2, C5, C3, Cz, C4, C6, CP1, CP2, P5, P4, Pz, P4, P6, A2. Inputs to the BCI electrodes over the sensorimotor cortices including, C3, C4, and Cz, were recorded in every session (Figure 1). EEG preprocessing steps include: 1) Digital filtering with a high-pass filter cutoff of 4 Hz, and a low-pass filter cutoff of 30 Hz. 2) Extraction and grouping of trials according to condition (rest, left/impaired hand movement, movement type (attempted), and the screening phase (Pre, Post intervention). This resulted in 10 trials for each of

condition/movement/screening phase combinations. 3) Identification and repair of bad (noisy) channels (via spline interpolation), followed by the removal of the three trials with the highest variance. The channel was identified as bad (noisy, poor connection, etc.) if the variance was <10 or >250 μV 2 in more than three trials. The units of the variance were those of the data squared: as the EEG data units were in μV, the variance units were squared μV. If more than four channels were identified as bad, the data for that session were removed from further analysis. At session level, this step resulted in 28 s of EEG data (7 trials × 4 s) for each condition/movement/screening phase combination set. 4) An average-reference montage was applied to the data (i.e., re-referencing from the original monopolar recordings). 5) Analyses with Fourier transforms computed using a multi-taper method (Thomson, 1982) (Mitra and Pesaran, 1999) at a 0.25 Hz resolution. This resulted in estimates of absolute spectral power sampled for every 1 Hz bin during the interval of 4– 30 Hz, and cross-spectral density. The trial length was 4 s and the resolution of Fourier transforms was 1/4 = 0.25 Hz.

Use of Brodmann Areas

To better illustrate the cerebral cortical sensorimotor areas represented by the co-registration of the 16-channel spectral EEG recordings to a three-dimensional head model space, we implemented ten regions of interest (ROIs). These ROIs are based on Brodmann's areas 1-7 (Brodmann, 1909), and coincide with the electrode placement in the standardized EEG cap (Figure 2). Regions of interests were defined as follows: ROI #1 = left BA 1-3 (primary somatosensory cortices); ROI #2 = left BA 4 (primary motor cortex); ROI #3 = left BA 5 (somatosensory association area); ROI #4 = left BA 6 (premotor cortices); ROI #5 = left BA 7 (visuomotor coordination area); ROI #6 = right BA 1-3 (primary somatosensory cortices); ROI #7 = right BA 4 (primary motor cortex); ROI #8 = right BA 5 (somatosensory association area); ROI #9 = right BA 6 (premotor cortices); ROI #10 = right BA 7 (visuomotor coordination area).

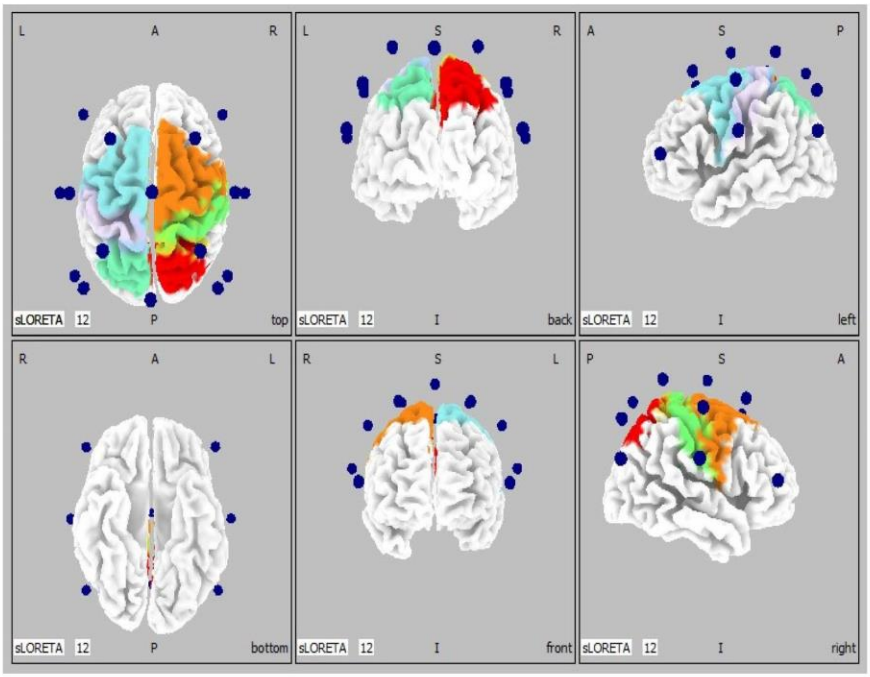

Figure 2: EEG electrode locations (n=16, blue spheres) are shown superimposed on a generic head model (left, middle, and right panels show top/bottom, back/front, and left/right views, respectively). BA, Brodmann's areas. Regions of interests (n=10) are defined as follows: ROI #1 = left BA 1-3 (primary somatosensory cortices, light purple); ROI #2 = left BA 4 (primary motor cortex, light blue); ROI #3 = left BA 5 (somatosensory association area, cyan); ROI #4 = left BA 6 (premotor cortices, light blue); ROI #5 = left BA 7 (visuomotor coordination area, cyan); ROI #6 = right BA 1-3 (primary somatosensory cortices, green); ROI #7 = right BA 4 (primary motor cortex, orange); ROI #8 = right BA 5 (somatosensory association area, red); ROI #9 = right BA 6 (premotor cortices, orange); ROI #10 = right BA 7 (visuomotor coordination area, red).

Source Localization (e/sLORETA)

Exact Low Resolution Electromagnetic Brain Tomography (eLORETA) is a weighted L2 minimum-norm distributed source localization algorithm used for the estimation of three-dimensional current density in the brain from the measured scalp EEG spectral data (Pascual-Marqui et al., 1994) (Pascual-Marqui, 2007). In the eLORETA (unit: μA/mm2.) implementation, computations are made in a realistic head model using the MNI152 template, with the three-dimensional solution space restricted to

cortical gray matter, as determined by the probabilistic Talairach atlas. The solution space consists of grey matter of the hemispheres and hippocampus (6239 voxels at 5mm grid in the MNI coordinate system). The specific frequency band cross-spectra (frequency-domain) obtained from the average-referenced scalp potential data, were the inputs for source localization. In summary, the cortical current density estimates from the 16 EEG electrode signals are assigned to an atlas space to obtain regions-of-interest (ROIs) based signals representing the source signals reflected in the recorded scalp EEG signal characteristics.

Overall, segments of clean EEG data (left/impaired hand movements and rest), separately for Pre- and Post-BCI intervention screening sessions, were used for the computation of cross-spectra (Mu [8-12 Hz] and Beta [18-26 Hz] bands). Averages of cross-spectra (1 average per each subject (n=16), separately for movements and rest trials) were computed, and then eLORETA estimates of Mu [8-12 Hz] band power at 6239 cortical locations/voxels were obtained, using subject-wise normalization of the estimates (which means dividing the eLORETA current density estimate values by the grand-average over all voxels and frequency bands evaluated). Finally, the derived (movement – rest) eLORETA normalized estimates were used in paired-sample statistics (using statistical nonparametric mapping approach (SnPM) as implemented in the s/eLORETA software; voxel-based comparison).

Source-localized ERD in cortical space was chosen as a means of representing scalp-recorded brain signal changes during attempted hand movements. Activity recorded on the scalp is a representation of multiple source generators within cortical space. Extrapolating from the scalp to cortical space provides the justification for examining Mu ERD, an accepted brain signal associated with planning and executing movement (Pineda, 2005), and offers a means for visualizing surface EEG recordings in three dimensions. In fact, estimated source signals are a better representation of the underlying cortical generators that produce the activity recorded by scalp electrodes (Yuan et al., 2008).

iCoh

Isolated effective coherence (iCoh) is a metric for frequency-specific directional flow of information transmission and offers a means of assessing direct paths of intracortical causal information flow of oscillatory activity. iCoh is based on formulating a multivariate autoregressive model from time series measurements and calculating the corresponding partial coherences after setting all irrelevant connections to zero, according to Pascual-Marqui (2014). From the spectral density matrix (bandwidth of 4-30 Hz, with spectral resolution of 0.25 Hz, including Mu [8-12 Hz] and Beta [18-26 Hz] ranges) obtained from estimated signals in the selected ROIs, the partial coherences between any pair of nodes/ROIs can be calculated. The t-statistics was performed for iCoh values between post and pre-intervention screening session trials of the impaired (left) hand movement with threshold set at $p=0.05$ ($t=2.13$, uncorrected for multiple comparisons).

Hand Grip Function

Hand grip strength was assessed with a dynamometer (Boissy et al., 1999). Participants were asked to squeeze the spring-loaded dynamometer lever as hard as possible (i.e. maximal single hand grasp) with their entire hand and then release. Three trials were performed with the affected hand and the average of the three trials was recorded as a handgrip score in pounds (lb).

Statistical Analysis

Statistical differences between post- and pre-intervention cortical estimates were tested using paired-sample t-statistics as part of the statistical nonparametric mapping approach (SnPM) implemented in the s/eLORETA software (voxel-based). Paired-sample t-statistics were also used to test differences in the ROI estimates (power and connectivity). Finally, the Pearson correlation coefficient was used to quantify the correlation between change in hand grip strength and change in Mu rhythm desynchronization (Post vs. Pre BCI intervention). The p values reported are uncorrected for multiple comparisons.

RESULTS

Localization of Mu ERD Changes Following BCI Intervention

Exact Low Resolution Electromagnetic Brain Tomography (eLORETA) was used to estimate the three-dimensional current density in the brain from the measured scalp EEG spectral data. In the eLORETA implementation, computations are made in a realistic head model using the MNI152 template, with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas.

The resulting distributions of ERD and ERS heatmaps of Figure 3 illustrate the distribution of ERD and ERS changes from Pre to Post BCI intervention in the n = 16 stroke survivors represented in Figure 4. Considering the distribution of ERS (red) and ERD (blue) voxels in Figure 3, it is apparent that as a result of BCI intervention, participants realized an increase of Mu ERD in ipsilesional hemisphere voxels of sensorimotor cortices during task performance (i.e., hand grasping) with the affected (left) hand compared to rest.

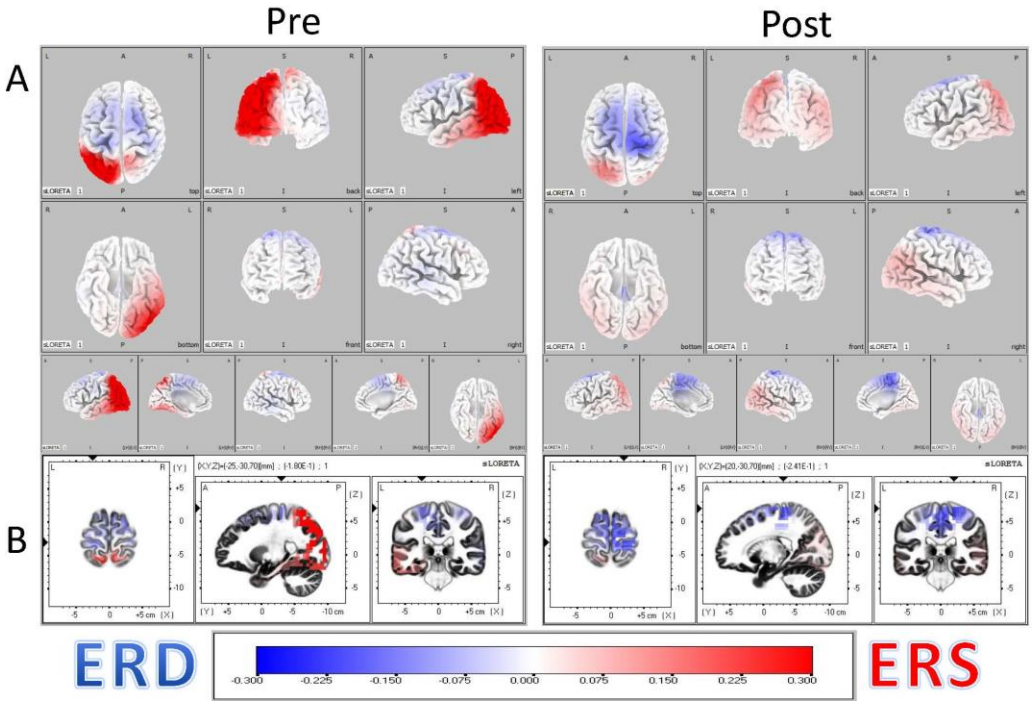

Figure 3: A: Localization of Mu rhythm desynchronization of cerebral cortical sensorimotor areas during movement of the affected hand compared to rest. Computations are made in a realistic head model using the MNI152 template, with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic

Talairach atlas. The specific frequency band cross-spectra (frequency-domain) obtained from the average-reference potential data were the inputs for source localization. The resulting distribution of ERD and ERS heatmaps illustrate the distribution of ERD and ERS changes from Pre to Post BCI intervention in the n=16 stroke survivors. **B:** Obtained eLORETA of Mu band power estimates at 6239 cortical locations (i.e., voxels) normalized across subjects.

Figure 4 shows pre-BCI intervention (blue) and post-BCI intervention (orange) computed eLORETA cortical spectral power estimates for the Mu [8-12 Hz] band (i.e., 1 average per each of the 16 subjects included in these sub analyses, separately for movement (left) and rest trials) for each of the ten regions of interest and assumed underlying Brodmann's Areas (Figure 2). ERD increases (post vs. Pre BCI intervention) were observed in regions of interest ROI #6 through ROI #9. The largest increases in Mu ERD were observed for regions of interest ROI #7 and ROI #8, which correspond to ipsilesional primary motor cortex (BA 4) (paired-samples t-test: p=0.11) and ipsilesional somatosensory association area (BA 5) (paired-samples t-test: p=0.056), respectively (Figure 4).

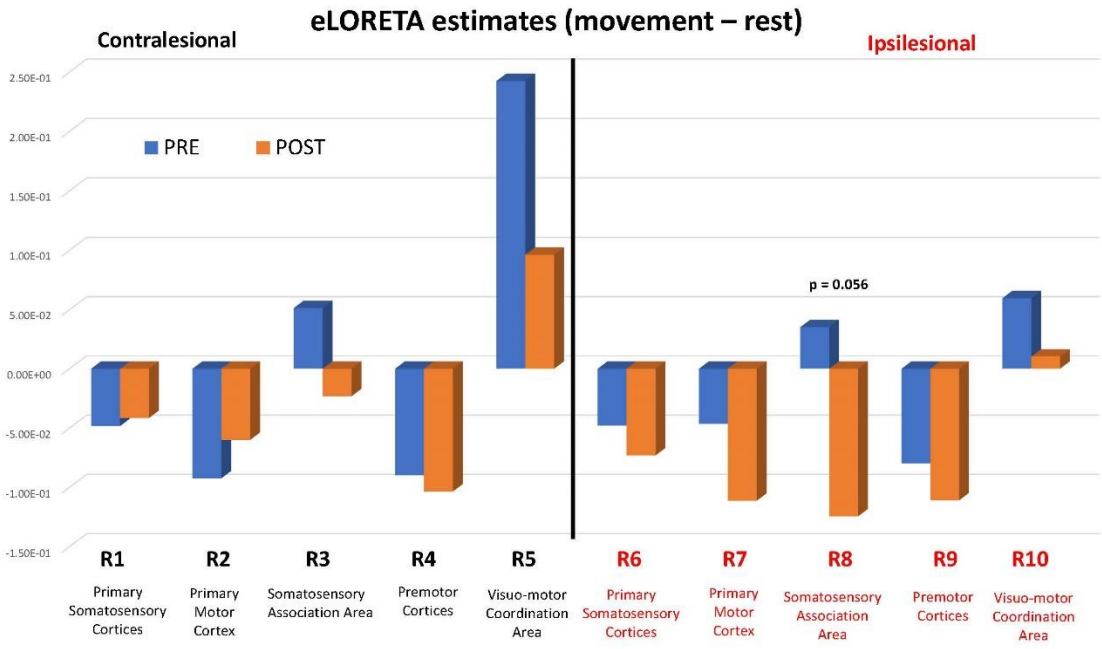

Figure 4: eLORETA estimates PRE (blue bars) and POST (orange bars) BCI intervention. eLORETA estimates between the two conditions [Movement – Rest] were based on measured EEG spectral power data in the Mu band [8-12 Hz] for each of the 10 regions of interest (ROI #1-10). P values refer to statistical group comparisons of Post vs. Pre estimates using a ROI-based one-tailed t-test. The p values reported are uncorrected for multiple comparisons.

Correlation Between Mu Desynchronization and Hand Grip Strength

Figure 5A plots change in hand grip strength as a function of change in Mu rhythm desynchronization (post vs. Pre BCI intervention) in the primary motor cortex of the ipsilesional hemisphere (ROI #7). Each data point represents an individual subject. Please note that negative numbers in the change in Mu rhythm desynchronization (i.e., Post-Pre), represent higher desynchronization in the Post phase. That is, larger negative numbers subtracted from smaller negative numbers will yield negative numbers. Improved hand grip function is positively correlated with increased Mu rhythm desynchronization (Post - Pre) in the ipsilesional primary motor cortex (Pearson's correlation coefficient $r = 0.435$, $p = 0.046$).

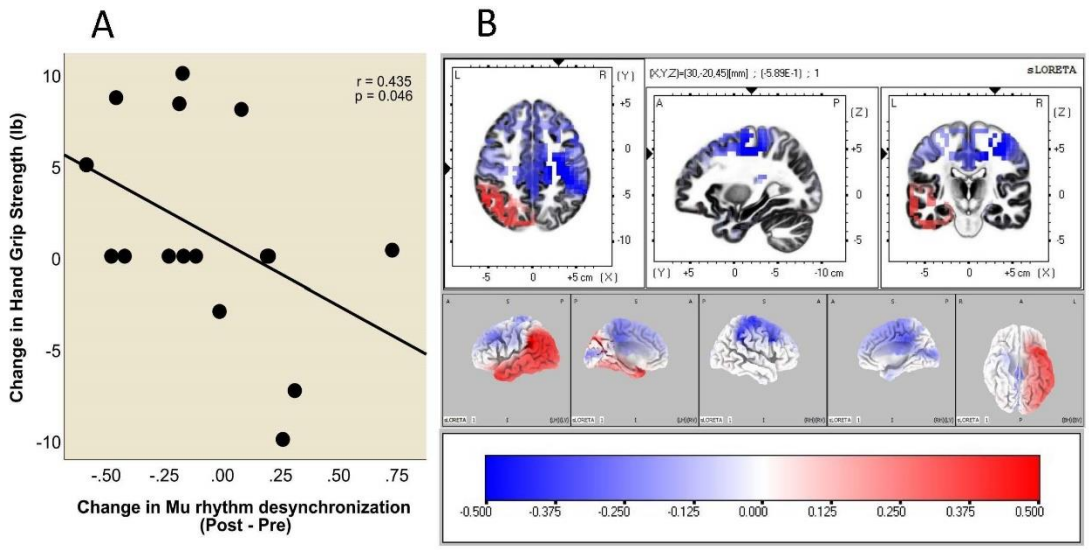

Figure 5: A: Increase in Mu rhythm desynchronization in ROI #7 (i.e., ipsilesional primary motor cortex), Post vs. Pre BCI intervention, is significantly correlated with increase in hand grip strength (Pearson correlation coefficient r=0.435, p=0.046). Two data points overlap at (-0.20, 0.00). **B:** Voxel-wise correlation of Hand Grip change with the Mu [8-12 Hz] rhythm desynchronization. The heat maps show colored r values (threshold set at r = 0.5). Scale: -0.5 (blue) to 0 (white) to +0.5 (red). Note that stronger ipsilesional (R) Mu rhythm desynchronization (negative values) (Post - Pre) correlates with larger increase in hand grip strength.

A voxel-wise correlation approach (refer to Methods section) was used to represent this relationship in brain atlas space (Figure 5B). The heatmaps show colored r values (e.g. Pearson's correlation coefficient values) and indicate that the correlation between improvement in hand grip strength and increase in Mu rhythm r values is strongest in voxels representing ipsilesional cerebral cortical sensorimotor areas.

In summary, the above results suggest that for the stroke-lesioned hemisphere, BCI intervention facilitates increased Mu desynchronization associated with movement rehabilitation of the impaired upper extremity.

Frequency-Specific Directional Flow of Information Transmission in Brodmann Areas 1-7

Direct paths of Pre to post BCI intervention frequency-specific flow of information transmission between cerebral cortical sensorimotor areas were analyzed by computing isolated effective coherence (iCoh) developed by Pascual-Marqui (Pascual-Marqui et al., 2014). Figure 6 plots iCoh values as a function of spectral frequency, Pre (blue) and Post (red) BCI intervention, to and from the 10 regions of interest (ROI #1-10) for the affected (left) hand. Mean values (Pre, Post) were compared via paired-sample t-stat, thresholded at t=2.13 [df=15], p=0.05 uncorrected).

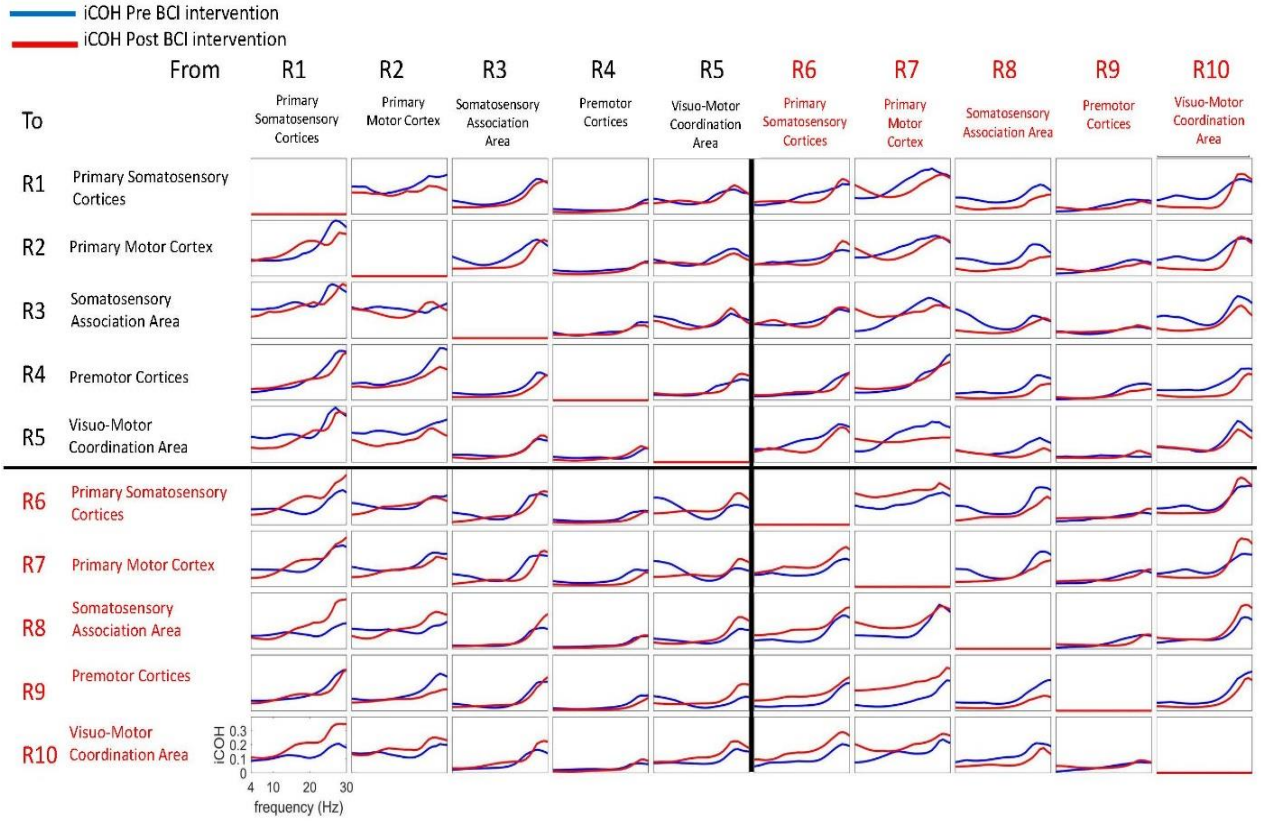

Figure 6: Isolated effective coherence (iCoh) - Frequency Specific Directional Flow of Information Transmission (Left Hand, Impaired Movement). Isolated effective coherence (iCoh), Pre (blue) and Post (red) BCI intervention. Vertical axis: 0 to 1. Horizontal axis: spectral frequency, 4 to 30 Hz. Columns are the senders, rows are receivers (i.e., FROM the top row of ROIs TO the horizontal columns of ROIs).

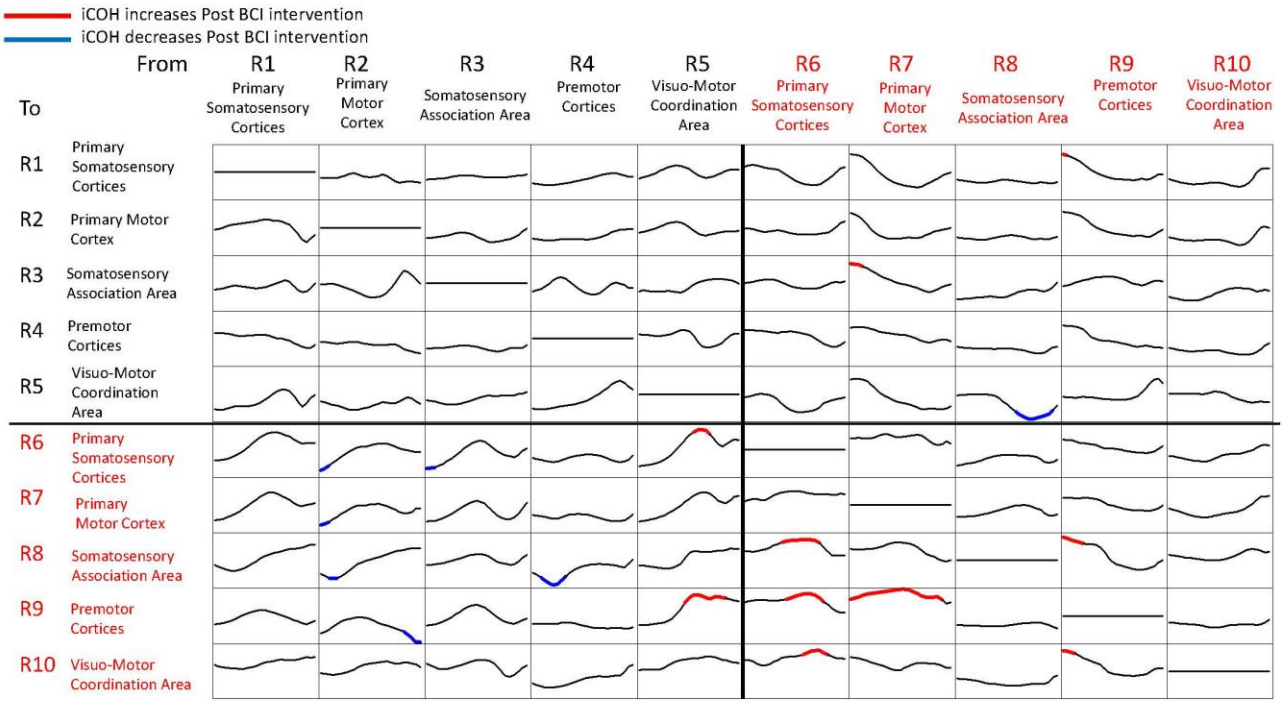

Figure 7: Plots of t-statistics for isolated effective coherence (iCoh) values Post vs. Pre BCI intervention of left (i.e., impaired hand) movement trials. Vertical axis: 0 to 1. Horizontal axis: spectral frequency: 4 to 30 Hz. Columns are the senders, rows are receivers (i.e., FROM the top row of ROIs TO the horizontal columns of ROIs). Red portions of the iCoh between two ROIs denote coherence increases at relative frequencies from Pre to Post, whereas blue portions denote significant decreases in iCoh from Pre to Post between two ROIs. Mean values (Pre, Post) compared via paired-sample t-statistics, with threshold set at t=2.13 [df=15], p=0.05, uncorrected for multiple comparisons.

Figure 7 summarizes t-statistics for the iCoh data shown in Figure 6. Statistically significant increases and decreases in iCoh at relative frequencies from Pre to Post BCI intervention between pairs of ROIs are plotted in red and blue, respectively. Significant increases in iCoh from Pre to post BCI intervention were seen going from ROI #7 to ROI #9, suggesting more causal informational flow is going from ROI #7 (ipsilesional primary motor cortex) to ROI #9 (ipsilesional premotor cortices) post compared to Pre BCI intervention. Significant decreases in iCoh were seen going from ROI #8 to ROI #5,

suggesting less causal informational flow is going from ROI #8 (ipsilesional somatosensory association area) to ROI #5 (contralesional visuomotor coordination area) post compared to Pre BCI intervention.

Signals in both Mu [8-12 Hz] and Beta [18-26 Hz] frequency ranges served as input commands in the present BCI design (Remsik, 2019b). Figures 8 and 9 summarize for Mu [8-12 Hz] and Beta [18-26 Hz] signal ranges, respectively, changes in functional connectivity of sensorimotor cerebral cortices during attempted movement of the impaired upper extremity as a result of BCI intervention. Each of the panels of Figure 8 and Figure 9 compares [Pre vs Post] iCoh values in Mu (Figure 8) and Beta (Figure 9) frequency ranges and represents a direct path of intracortical causal information flow of oscillatory activity between two ROIs. Statistically significant differences between pre (blue bars) and post (red bars) iCoh values between pairs of ROIs are represented by surrounding boxes with blue denoting significant decreases in iCoh, and red boxes signifying significant increases in iCoh.

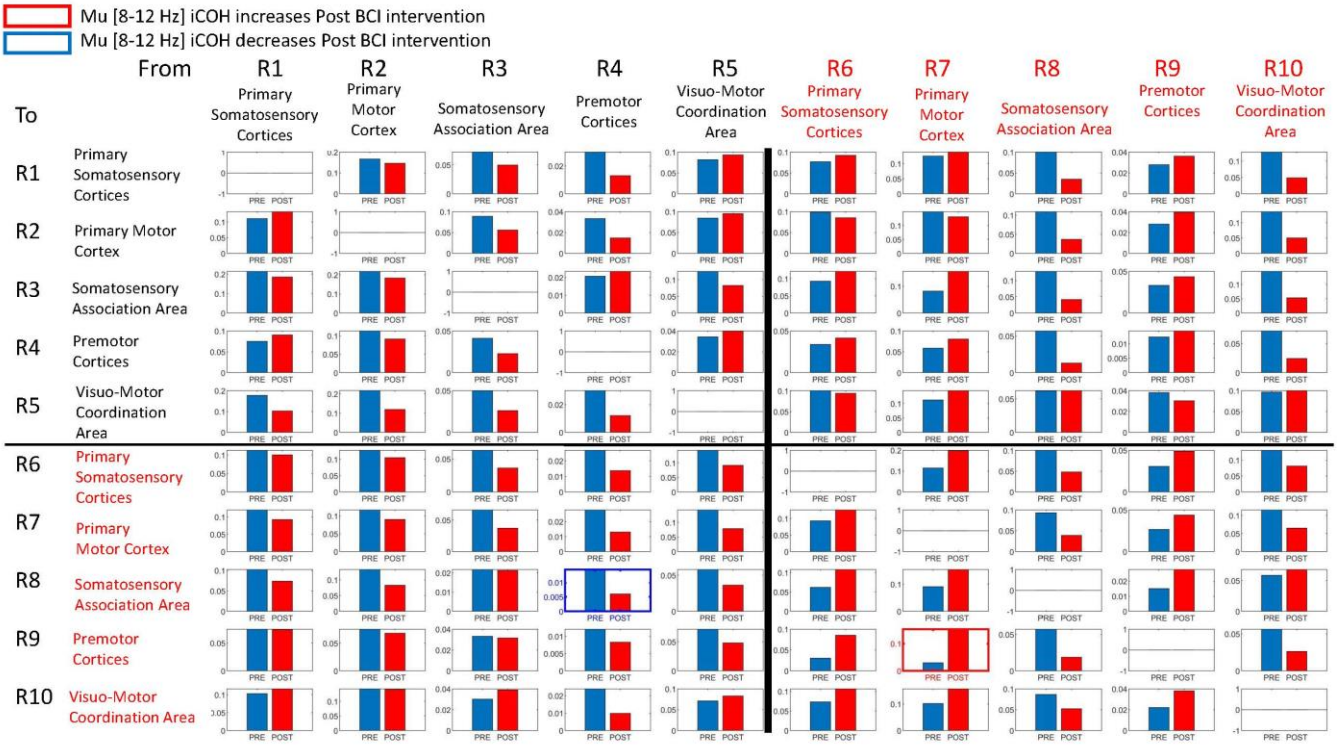

Figure 8: Plots of iCoh between two given ROIs in the Mu (μ) frequency band [8-12 Hz], Pre and Post BCI intervention. Vertical axis: Coherence value -1 to 1. Horizontal axis: Pre (blue) and Post (red). Columns are senders,

rows are receivers (i.e., FROM the top row of ROIs TO the horizontal columns of ROIs). Blue surrounding boxes indicate significant decrease in iCoh while red surrounding boxes denote significant increases in iCoh (Post vs. Pre).

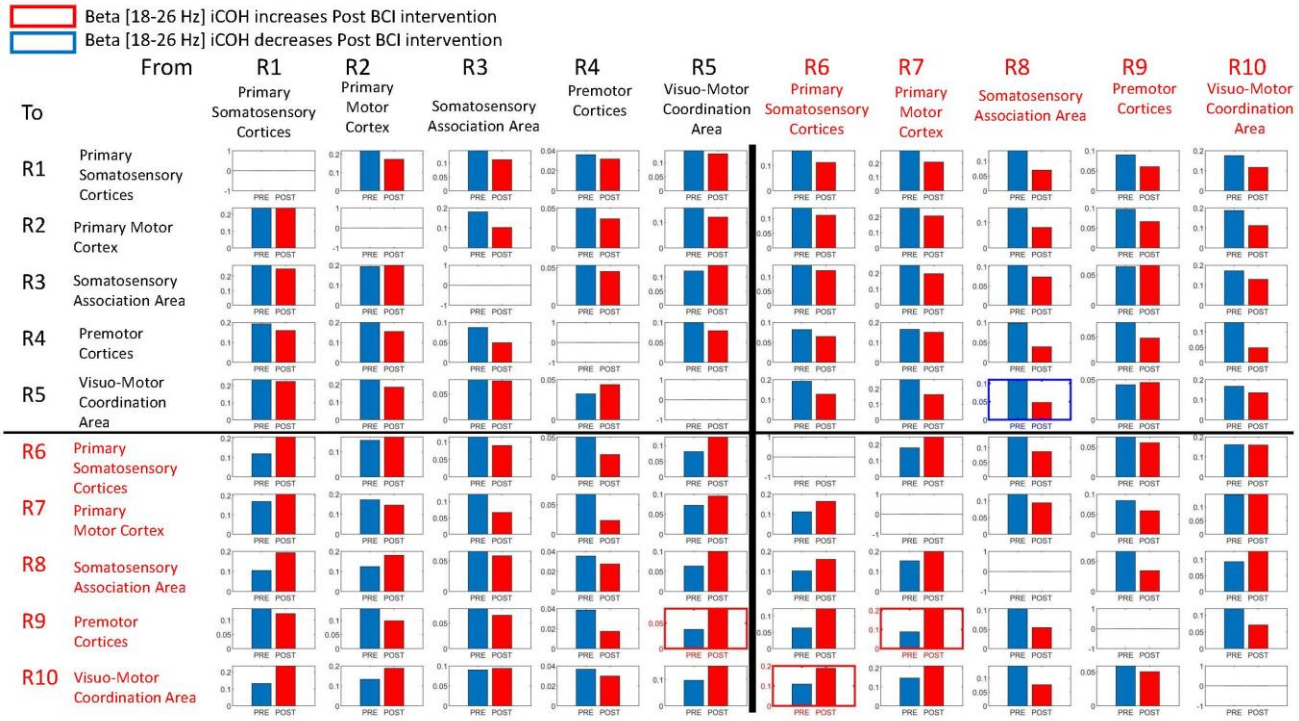

Figure 9: Plots of iCoh between two given ROIs in the Beta (β) frequency band [18-26 Hz], Pre and Post BCI intervention, Vertical axis: Coherence value -1 to 1. Horizontal axis: Pre (blue) and Post (red). Columns are senders, rows are receivers (i.e., FROM the top row of ROIs TO the horizontal columns of ROIs). Blue surrounding boxes indicate significant decrease in iCoh while red surrounding boxes denote significant increases in iCoh (Post vs. Pre).

In the Mu [8-12 Hz] frequency band, iCoh values significantly decreased pre vs post BCI intervention from ROI #4 (contralesional premotor area) to ROI #8 (ipsilesional somatosensory association area) (Figure 8). Mu band iCoh values significantly increased pre vs post BCI intervention from ROI #7 (ipsilesional primary motor) to ROI #9 (ipsilesional premotor cortices).

In the Beta [18-26 Hz] frequency band, iCoh significantly decreased Pre vs. post BCI intervention from ROI #8 (ipsilesional somatosensory association area) to ROI #5 (contralesional visuo-motor coordination area) (Figure 9). Beta band iCoh values significantly increased Pre vs. Post BCI intervention from ROI #5 (contralesional visuo-motor coordination area) to ROI #9 (ipsilesional premotor cortices), from ROI #6 (ipsilesional primary somatosensory areas) to ROI #10 (ipsilesional visuo-motor coordination area), and from ROI #7 (ipsilesional primary motor cortex) to ROI #9 (ipsilesional premotor cortices) (Figure 9).

DISCUSSION

We have investigated potential neural substrates underlying the effect of BCI intervention on motor recovery in stroke survivors. Here we report, for grasping movements of the affected hand compared to rest, significantly greater desynchronization of sensorimotor rhythms in the Mu frequency band [8-12 Hz] recorded via scalp electrodes in the ipsilesional hemisphere, indicating greater activation of the ipsilesional sensorimotor system following BCI intervention. Moreover, we demonstrate that the increased Mu desynchronization in the ipsilesional primary motor cortex, Post vs. Pre BCI intervention, correlates significantly with improvements in hand function as assessed by grip force measurements. Furthermore, analyses of frequency-specific directional flow of information transmission between cerebral cortical sensorimotor areas, deduced from measurements of isolated effective coherence (iCoh), revealed both intra- and interhemispheric changes as a result of BCI intervention, in particular, increased functional connectivity from ipsilesional primary motor to ipsilesional premotor cortices, and from contralesional visuo-motor coordination area to ipsilesional premotor areas, respectively.

A growing body of evidence supports the effectiveness of EEG-based BCIs on improvement of upper extremity motor function following stroke (for meta-analyses/reviews see: (Cervera et al., 2018) (Bai et al., 2020) (Simon et al., 2021)). BCI paradigms utilizing FES and/or attempted voluntary movements of the hemiparetic hand are particularly promising interventions for the rehabilitation of stroke survivors (Ramos-Murguialday et al., 2013) (Kim et al., 2016) (Biasiucci et al., 2018) (Nishimoto

et al., 2018) (Tabernig et al., 2018) because they may induce and/or facilitate neuroplastic changes, at both structural and functional levels, that link movement intention with muscle contraction (Daly and Wolpaw, 2008) (Ramos-Murguialday et al., 2013) (Biasiucci et al., 2018) (Bai et al., 2020).

Source Localization of Mu ERD in Sensorimotor Cortices

In a less tightly controlled analysis of available NCT02098265 participants at the time, our laboratory demonstrated (Remsik et al., 2019) that ipsilesional Mu [8-12 Hz] ERD increases, recorded over cerebral cortical sensorimotor areas by scalp electrodes C3/C4 (Figure 1), were correlated with motor recovery of the affected upper extremity in stroke survivors. Here, we confirm and expand upon our previous findings in three ways. First, we present a more detailed source mapping to cortical space of Mu rhythm desynchronization and show that motor recovery is predominantly associated with Mu ERD changes ipsilesionally, near the primary motor cortex (Brodmann Area (BA) 4) and somatosensory association area (BA 5) (Figure 3). Second, we show that greater Mu desynchronization in ipsilesional primary motor cortex (BA 4) is significantly correlated with improvement in hand grip strength, an objective, quantitative measure of UE function and capacity, following BCI-FES intervention (Figures 4 & 5). Third, we show evidence of functional connectivity changes between ipsilesional sensorimotor cortices following BCI-FES intervention, which is consistent with the view that BCI-FES use supports and/or engages fundamental neural mechanics that link volitionally controlled EEG signal changes with changes in objective behavioral measures of motor function and capacity. Such mechanisms may be specific to motor recovery (Biasiucci et al., 2018) (Bai et al., 2020) and/or may be signatures of motor learning in general (Yuan et al., 2008) (Edelman et al., 2019).

Our results are in line with findings of other studies that have employed similar BCI paradigms in cohorts of stroke survivors with similar demographics (Daly et al., 2009) (Ramos-Murguialday et al., 2013) (Ang et al., 2014) (Ono et al., 2014) (Popovic, 2014) (Hu et al., 2015) (Kim et al., 2016) (Biasiucci et al., 2018) (Nishimoto et al., 2018) (Tabernig et al., 2018) (Bai et al., 2020) (Simon et al., 2021). For example, Biasiucci (2018} report that only their BCI-FES group exhibited significant functional

improvement following BCI intervention. Our result that increased ipsilesional Mu desynchronization is significantly correlated with increased grip strength is in good agreement with the finding of Biasiucci (2018} that only their BCI-FES group exhibited a significant and lasting increase of the strength of the muscle targeted by the FES (in their study: extensor digitorum communis, which elicits full extension of the wrist and fingers). Furthermore, our result that SMR desynchronization is largely ipsilesional, indicating greater activation of the ipsilesional motor system following BCI-FES intervention, is in keeping with previous reports in stroke survivors (Mihara et al., 2013) (Li et al., 2014) (Biasiucci et al., 2018) (Bai et al., 2020). BCI-FES devices may interface with native underlying mechanisms of neuromotor plasticity and control that have been demonstrated to engage and facilitate brain changes and behavior changes indicative of clinical motor recovery.

Functional Connectivity and Motor Recovery

Importantly, although voxel-wise distribution of eLORETA output revealed a sensorimotor-centered focus of Mu ERD change associated with motor recovery, ipsilesional-focused Mu ERD change may not be the sole driver of motor recovery in stroke survivors using a BCI. Mu signal changes in cortical sensorimotor areas may be part of a broader integration of disparate ROIs in a neural network that includes both intra- and interhemispheric components (Figures 8 & 9), although recovery of the primary motor region has been demonstrated to be essential to motor recovery (Grefkes and Fink, 2014; Volz et al., 2014). Therefore, we sought to understand whether the underlying neural network is specific to localized neural populations represented by the Brodmann's area segmentations or, whether there is a larger geography of populations – functionally connected neural networks – that may be influenced by participation in the BCI intervention. We used discrete data in time series to represent directionality or sequencing of activity associated with these changes to test the hypothesis that BCI intervention results in changes in frequency-specific directional flow of information transmission (functional connectivity) in ipsilesional and/or contralesional sensorimotor areas (Ward et al., 2003a) (Rehme et al., 2011a; Rehme et al., 2011b; Rehme et al., 2012) (Dubovik et al., 2012) (Várkuti et al., 2013b) (Nicolo et al., 2015) (Pichiorri et al., 2015) (Pundik et al., 2015) (Wu et al., 2015) (Biasiucci et al., 2018).

The changes in functional connectivity reported here, particularly between ipsilesional primary motor cortex and ipsilesional premotor cortices, agree with previous studies that have employed comparable BCI designs (Wu et al., 2015) (Biasiucci et al., 2018). Increased interactions between ipsilesional motor brain areas are associated with better recovery and motor performance (Dubovik et al., 2012) (Nicolo et al., 2015) (Wu et al., 2015). The change in effective connectivity between ipsilesional motor cortex and premotor cortices following BCI intervention was observed for both Mu and Beta frequency ranges in both the present results (Figures 8 & 9) and those of Biasiucci (2018}, which is consistent with the view that the functional improvement following BCI intervention is due to facilitation and induction of neuroplastic changes associated with motor recovery as well as motor learning more broadly.

BCI-FES and Motor Recovery

BCI-mediated FES leads to the most significant recovery of motor function following stroke (Bai et al., 2020) (Simon et al., 2021). The inclusion of FES is thought to contribute to the clinical effect of a BCI not only through the somatosensory contribution of facilitated muscle stimulation but also through pairing of volitionally modified CNS efferent signals with stimulation (i.e. activation) of the impaired distal muscle (Bergquist et al., 2011). Biasiucci (2018) have demonstrated through their BCI-FES versus sham FES experimental design that it is not the FES alone but rather the contingency between rich sensory feedback and suitable activation of cortical motor areas that may drive activity-dependent, Hebbian plasticity that may underlie motor recovery in BCI-FES interventions. Whereas our study design does not allow us to draw the same conclusions as Biasiucci (2018) with respect to the clinical significance of the FES adjuvant, both our results and BCI-FES device are similar to those of Biasiucci (2018). Therefore, it is likely that the clinically relevant functional gains demonstrated here are due to the same strict contingency of BCI-driven FES detailed by Biasiucci (2018).

Future research is needed to better identify and track the genesis and progression of neuroplastic changes, and to determine the relative importance of the various intra- and interhemispheric network connectivity

changes presented here. In addition, further research is necessary to discover the mechanistic origins of any such neuroplasticity, and how such mechanism(s) may improve rehabilitation strategies that enable caregivers to provide maximal benefit to patients (Bai et al., 2020) (Simon et al., 2021).

Limitations

Localizing cortical neuronal signatures with EEG scalp electrodes is a process that neuroscience researchers and others have used for some time (Pascual-Marqui et al., 1994) (Pascual-Marqui, 2007). It is generally believed that higher density electrode arrays in the EEG cap provide more reliable and accurate localization estimations of the underlying neurophysiological processes. The use of eLORETA in a 16-channel cap arrangement, in non-research settings, likely pushes the boundaries of this method's practical limits as an estimation tool for source localization of motor-EEG brain signals. Co-registration of spectral EEG data to MNI atlas space is a first step towards addressing this issue. In this work, scalp electrodes, while limited in number (16 channels), specifically covered sensorimotor cortices with greater density than the conventional 10-20 electrode placement system. Arguments can also be made for the use of 'individualized' head modelling over 'standard' head models. The use and reference to Brodmann's areas in this work are intended solely as representative labels of the brain segmentations proposed by Brodmann, and we assume that these areas are generally emblematic of the functional cortical brain areas recorded by the scalp EEG electrodes of this cap arrangement (Figure 1).

In future research, repeating or initiating a similar BCI study with high density or 19 channel standard electrode arrays might allow a stricter evaluation of the 'boundaries' in channel count and 'electrode density as spatial coverage over areas of interest' by comparing the source localization results from these findings to the aforementioned high- and low-density electrode setups (i.e., with 'full' head coverage). With any channel count placed 'strategically' with higher density than the basic n=19 (i.e.,10-20 system) over local functional network areas of interest on the scalp, reliable recordings of neuro-electrophysiological functioning might be feasible.

CONCLUSION

The results of the present study are consistent with the view that EEG-based BCI intervention enhances information flow between cerebral cortical sensorimotor areas involved in motor planning, motor execution, and motor learning, and as such aides in establishing BCI intervention as an effective therapy for motor rehabilitation of stroke survivors.

BCI intervention may help facilitate adaptive brain changes, such as increased ERD during movement of the impaired upper extremity in the stroke-lesioned brain, but it is the brain's ability to adapt its functional connections (i.e., plasticity of the sensorimotor system) that may underlie the potential of BCI intervention as a rehabilitation strategy.

In conclusion, this study not only helps to establish the efficacy of BCI-FES intervention as a therapy for stroke survivors but is also important for increasing our understanding how sensorimotor processing contributes to the transformations of plans for voluntary limb movements into muscle commands necessary for their execution in healthy individuals. Thus, the results have the potential to guide development of innovative strategies for motor rehabilitation and are also important for increasing understanding of motor control in general.

Chapter 6
Discussion

The central hypothesis underlying this dissertation is that brain-computer interface devices that use contingent muscle activation and sensory-based performance feedback are useful for the clinical rehabilitation of poststroke upper limb hemiparesis, and they offer a means to study how recovery occurs in the brain. Investigating the clinical efficacy of BCI-FES enables the study and development of more effective treatments for poststroke hemiparesis and provides a model within which to expand science's understanding of the neuromechanical processes of motor control, motor learning, and the processes of neural recovery more broadly. This dissertation presents evidence of efficacy of this multimodal BCI-FES design for the treatment of upper extremity physical impairments resulting from brain injury induced by stroke, and details a number of clinically relevant techniques for continued study of neuromechanical processes of motor learning and recovery, delivered by brain-based interventions that leverage existing neuroarchitecture and native neuroplastic processes to improve brain connectivity and ultimately, functional motor capacity. Understanding the processes by which poststroke motor recovery is possible will require an investigation of the functional and plastic capacity of the lesioned hemisphere -- the native control center of the stroke-impaired upper extremity -- as well as the relative contributions of ipsilesional, perilesional, and contralesional brain areas as well as the level to which functional connectivity of the bihemispheric sensorimotor system impacts the recovery process. These research questions and efforts were worth pursuing for the betterment of stroke survivors' quality of life as well as the advancement of understanding and knowledge in science.

Aim 1 seeks to establish the clinical efficacy of multimodal BCI-FES for treatment of upper extremity hemiparesis poststroke and whether factors at baseline and BCI usage (i.e., dose) impact recovery potential. Aim 2 seeks to establish whether brain signal changes in the lesioned hemisphere are reliable markers of recovery and whether they track with or drive behavioral improvements over time. Aim 3 seeks to establish the relative contributions of the lesioned and non-lesioned hemispheres and to

identify any patterns of functional connectivity change associated with multimodal BCI-FES use and motor recovery.

KEY FINDINGS

The data presented in Chapter 3 and Chapter 4 suggest that BCI-FES intervention is an efficacious means of delivering poststroke motor recovery to participants of varying stroke etiology, chronicity, and level of resulting motor impairment. Evidence from this study suggests that, to date, 64% of participants realized measurable functional improvement in their stroke-impaired upper extremity. Of those individuals, 43% realized clinically meaningful gains in motor recovery as measured by the ARAT. In Chapter 3 evidence of efficacy shows that participants also frequently demonstrated continued and often increased improvement levels between the completion of therapy timepoint, and the one-month follow up timepoint in both objective and subjective measures of motor function poststroke. This finding suggests that multimodal BCI–FES intervention resulted in a statistically significant, clinically relevant, and lasting reduction of UE impairment in some stroke survivors and that these users were able to continue to improve upon meaningful gains realized during intervention, even after administration ceased.

Chapter 3 also presents evidence of recovery of function as measured by significant improvements to various clinical outcome measures and self-report measures beyond the primary outcome measure, ARAT. The Stroke Impact Scale sub scores of affected handgrip strength and mobility were consistently found to measure statistically significant adaptive change over time, something that was not always captured by ARAT improvement scores for the same participants. These results propose that multimodal BCI-FES effects are distributed in nature. This suggests that metrics of stroke-related motor impairment, such as the ARAT, may not be sufficiently sensitive to BCI-driven motor changes and might fail to capture subthreshold changes that ultimately manifest as meaningful capacity or functional changes for the stroke survivor.

The data presented in Chapter 4 support the theory that behavioral changes are associated with adaptive brain changes, specifically in the Mu (μ), and Beta (β) frequency bands. Significant changes in

ERD as a result of BCI-FES intervention were observed localized to the lesioned hemisphere, at electrode locations near to and representing primary and supplementary motor areas (i.e., electrodes C3/C4). Evidence presented in Chapter 4 also suggest that improvements in primary and secondary outcome measures of behavior were strongly associated with these same changes in task-related brain signals (i.e., ERD) that were localized in the ipsilesional hemisphere.

The analysis presented in Chapter 5 identifies that both intrahemispheric, and interhemispheric connectivity changes occur with BCI-FES intervention. These data suggest functional connectivity shifts to ipsilesional primary motor cortex and supplementary motor areas following BCI-FES intervention from sources that are both intrahemispheric and interhemispheric. Despite clear evidence of contralesional contributions to functional connectivity changes, it is less clear whether these contralesional changes -- as compared to the adaptive ipsilesional brain activity and functional connectivity changes, have on resulting motor capacity increases as a result of multimodal BCI-FES intervention.

INTERPRETED RESULTS

With regard to Aim 1, and in agreement with recent metanalyses and clinical evidence, the results presented here suggest that multimodal BCI-FES intervention is an efficacious means of delivering motor rehabilitation poststroke (Cervera et al., 2018) (Bockbrader et al., 2018) (Bai et al., 2020) (Simon et al., 2021) (Biasiucci et al., 2018). At the cohort level, a significant effect of time on ARAT improvement ($p = 0.046$) was observed. Analysis of these data showed cumulative duration of BCI-FES intervention of up to 30 hours impacts ARAT scores with an average change between timepoints of 0.64 ARAT-points (max ARAT score = 57 points), representing meager but positive cohort level improvement as a result of intervention. Moreover, several self-report measures ($SIS_{mobility}$, SIS_{adl}, and $SIS_{strength}$) as well as two objective measures of hand function and capacity, 9-hole peg test and dynamometer measured grip strength, were also significantly affected by time in BCI-FES intervention. These findings between

baseline and completion of BCI were found to persist at one-month follow up, which suggests that BCI-FES intervention results in lasting improvements in motor function.

The likelihood ration test of the LME models shows that time in intervention is an important factor in recovery, even out to the follow-up timepoint, suggesting BCI-FES results in lasting adaptive effects. Outcome improvements between the intervention and control conditions were not significantly different, which suggests that a subset of participants drive the measured cohort-level improvement whereas another subset of participants do not realize adaptive or beneficial changes as a result of BCI-FES intervention. Of course, other factors may also account for and/or contribute to this variability.

It is important to understand the complex interactions between BCI-based rehabilitation and a number of factors, including: the location of lesions, the residual motor function at trial onset, the latency between neural activity and external stimulation, the type of neural activity used for BCI control, the duration and volume of BCI training, and the combination of BCI training with additional therapies to enhance plasticity. Through well-designed and well-implemented studies to determine the roles of these factors, it will be possible to further develop and translate BCI systems into tools to improve patients' lives. Mechanisms of neuroplasticity during the post-stroke recovery period, either through spontaneous recovery or through traditional rehabilitative approaches (Saur and Hartwigsen, 2012) (Cramer and Riley, 2008) (Ward et al., 2003a) were once thought to be time-limited (Zeiler and Krakauer, 2013). The results presented here suggest, however, that additional recovery is still possible for many stroke survivors through either alternate mechanisms that emerge during rehabilitation or through simple persistent practice well after their stroke insult. In order to identify whether baseline factors might be the cause of these disparities between individual responses, cohort participants were grouped *post hoc* into responders, and non-responders.

Upon further examination of the differences between individuals, *post hoc* responder and nonresponder groups were found not to significantly differ from one another according to expectations derived from previously published research. Prior evidence suggests that stroke survivors with limited

time since stroke and moderate to mild levels of impairment realize the greatest therapeutic benefit (Zeiler and Krakauer, 2013) from BCI interventions(Remsik et al.); however, in these post hoc grouped data, responders were more likely chronic and severely impaired individuals (Remsik et al., 2018). One finding from these experiments that may account for this disparity between what an expected responder looks like compared to evidence of actual responders under this design is that more time spent using the BCI (i.e., more BCI runs) was found to correlate strongly with UE recovery as well as brain signal changes associated with motor recovery. Another finding from these data suggests that of those participants with room for improvement, most realized meaningful intervention-related gains in both physical and neurological measures. It is also possible that those participants without room for improvement (i.e., those with ceiling effect) or in other words, those who were so mildly impaired that they scored a full 57 out of 57 points score on the primary outcome measure, ARAT, may have skewed the expected result at the cohort level -- that mild impairment and less chronic participants realize greatest physical gains following intervention. While continued improvement for those participants with ceiling factors was not measurably possible, it is important to note that none of them recorded a decrease in motor capacity at any timepoint during or after the intervention. Further, this cohort is currently heavy with chronic and severely impaired stroke survivors and interpretation of the results may be limited by the insufficient sample size as prescribed by the power analysis, which identified a need for 99 participants, of which, by the time of this dissertation, only 44 have been measured.

These encouraging findings of recovery are corroborated by the comparison of measured ARAT changes between the control period and those of the intervention period. While there was not a statistically significant difference between the rate of change of either treatment condition, as presented in Chapter 3, the intervention treatment condition saw greater change between study timepoints compared to the control condition. More research using more tightly constrained demographic and treatment factors is needed to further address these research questions as the study design presented here is not capable of assessing such relationships in a suitably controlled manner.

These data suggest that multimodal BCI-FES use, in agreement with published literature, has the ability to drive functional motor recovery in this patient population and that participant factors may not significantly limit a user's ability to realize functional improvement in a stroke impaired UE when using this BCI-FES design, as prior evidence suggests. Data presented here support this as factors identified by others that might impact recovery (e.g., age, chronicity, severity, concordance – whether the stroke impacts the individual's dominant hand –) were not found to be significantly predictive of recovery in this cohort. Rather, the amount of time spent using the BCI-FES device may be a more meaningful predictor of motor recovery than presenting biological factors or behavioral capacities at baseline, as was evidenced in this study.

Importantly, BCI-based treatments allow rehabilitation of stroke survivors to commence during crucial (early) time windows poststroke, as well as long after initial insult, and provide alternatives for more severely impaired individuals or those who have not yet regained any overt movement capacity and, therefore, may not be able to benefit from traditional physical therapies. Of those participants with room for improvement in the primary outcome measure, 64% recovered some level of motor function, following BCI-FES use, and no participants significantly decreased their motor capacity, as evidenced by ARAT scores.

With regard to Aim 2, after a stroke, movement-related neural activity is altered in a variety of ways (Pfurtscheller et al., 1984) (Honda et al., 1997) (Green et al., 1999a; Green et al., 1999b) (Buch et al., 2012). Remodeling of perilesional areas has been associated with improved function after stroke (Nudo et al., 1996b) (Turton et al., 1996) (Netz et al., 1997; Ward et al., 2003a; b). As in the present study, previous BCI applications for rehabilitation after stroke have focused on brain areas of the affected hemisphere for BCI control (Buch et al., 2008) (Daly et al., 2009) (Ramos-Murguialday et al., 2013); however, examples of ipsilateral (i.e., ipsilesional) controlled BCIs exist as well (Bundy et al., 2012). Whereas ipsilateral controlled BCIs have been demonstrated to be effective and mildly therapeutic, the data presented here suggest that task-relevant changes in ipsilesional brain function, that is, changes to the

functioning of native neuroarchitecture and connectivity, yield significant and meaningful behavioral improvements of the stroke affected UE. Further, many BCI designs utilize motor imagery or imagined movements of the impaired extremity to drive BCI use. Using a similar assumption that rehabilitation of the impaired brain and resulting motor function must focus on rehabilitation of the functional capacities of the impaired brain areas and connections responsible for hemiplegia, the present BCI-FES utilized actual or attempted movements of the stroke-impaired hand to drive BCI engagement. More evidence and more tightly controlled factor analyses are needed to determine if attempted movements, as compared to imagined movements, recorded from the ipsilesional hemisphere, as compared to the contralesional hemisphere, are superior strategy designs given the rehabilitative goal of any such device or technique. The pervading assumption remains, however, that trained use of native brain areas with native brain and upper extremity motor function will result in the greatest level of recovered function for stroke survivors with persistent UE hemiplegia resulting from stroke.

The data presented in Chapter 4 suggest that the quality of baseline task-specific brain activity directly correlates with impairment level at baseline, that is, baseline brain activity during task performance is predictive of the level of physical impairment resulting from stroke. This association directly links quality of ipsilesional brain function (as measured by Mu and Beta r-squared values of attempted hand-movements during the first intervention session) with level of stroke-related motor impairment (as measured at baseline, pre-BCI intervention). This report presents the first known association of these two baseline factors as studied in a BCI-FES intervention design for persistent UE hemiplegia resulting from stroke insult. Table 3 of Chapter 4 demonstrates that baseline Beta ERD is a good indicator of functional motor capacity; less Beta ERD is associated with more severe impairment. Thus, ipsilesional task-specific brain signal changes (e.g., ERD) positively correlate with changes in behavior following BCI intervention.

Specifically, during attempted movements of the impaired hand, desynchronization levels in ipsilesional Mu and Beta frequency bands positively correlated with behavioral scores and thus suggests a

potential mechanism of BCI intervention: a link between electrophysiological brain signals and behavior. Statistically significant increases in ipsilesional Beta ERD resulting from more BCI runs and increases in ipsilesional Mu ERD relating to increased functional recovery, suggest that BCI-FES training of ipsilesional brain areas with attempted movements of the stroke-impaired hand results in meaningful clinical improvements following BCI-FES intervention. While evidence exists that BCIs can be controlled by a contralesional design (Bundy et al., 2018), these findings support the theory that intervention in the lesioned hemisphere will not only result in effortful BCI-FES control but will also yield meaningful clinical improvements of the impaired UE, in addition to facilitating BCI-FES use. This hypothesis is further supported by observations that associations of task-specific brain signal changes were measured during attempted but not during imagined movements of the impaired. Thus, relevant task-specific gains measured in behavioral outcomes may be a consequence of challenging and rewarding (actual) movements associated with ADLs, which the participants previously may have thought to be impossible or too difficult to produce successfully.

BCI-FES intervention may help challenge a survivor's individual conception of their behavioral and physical limitations by pushing the participant, perhaps for the first time in a while, to use the affected hand and rewarding them (according to an anticipatable, clear, and consistent schedule) for doing so. This theory may explain the minimal behavioral gains observed by most participants, in comparison to the significant gains obtained by some, and their absence in others, and that such findings may be related to the encouragement of attempting previously ineffective motor behaviors. The statistically significant gains observed, supported by the higher incidence of significant changes to subjective measures than objective measures of motor function may result from the specific reward structure of this multimodal BCI-FES intervention design in addition to, or more so than, any reliable neuromechanical or electrophysiological contributions. Further evidence is needed to determine the relative contributions of task type to the nature of resulting behavioral gains.

With regard to Aim 3, the sensorimotor system is a highly interconnected, bihemispheric network that is plastic in nature and is capable of adapting existing capacities toward new functional abilities or improved capacities through reinforced learning. Conditioning -- learning a new behavior through association and reinforcement -- is a primary mechanism for developing and refining motor skills and is thought to underly the effectiveness of BCI interventions (Biasiucci et al., 2018). It is thought that BCI device effectiveness can be explained by conventional learning theories and replication of analogous BCI-driven motor learning outcomes observed in the healthy brain (Wolf et al., 2008; Young et al., 2014a; Young et al., 2014c). BCIs provide real-time feedback to the user and reward consistent production of neural features concordant with native (i.e., normal) hand motor function. Therefore, apparent changes in functional cortical activation patterns may persist after therapy when attempting tasks similar to those trained with BCI therapy (Young et al., 2014c) (Bundy et al., 2012). In this multimodal BCI-FES design, conditioning and subsequent motor learning operates on the principle that targeted functional cortical activation of sensorimotor areas should result in task completion, or at least, facilitated motor output, and insufficient activation and subsequent absence of reward (e.g., task completion, goal attainment) should not produce any significant change in behavior. This theoretical knowledge supports the possibility of inducing lasting brain changes through a BCI system and regimen that result in observable motor capacity improvements. However, exactly what the necessary functional connectivity changes induced in stroke patients with lasting recovery of hemiparesis are remains unclear, though mechanisms and strategies have been proposed (Soekadar et al., 2014) (Christensen and Grey, 2013) (Biasiucci et al., 2018).

The theory of BCI-induced neuroplasticity (Soekadar et al., 2011; Soekadar et al., 2014) (Bach-y-Rita, 1981; 1990; Muralidharan et al., 2011) posits that the amount of reinforcement and the timing or schedule of reinforcement can significantly impact the efficiency and specificity of learning (Young et al., 2015) and thus, the resulting extent of motor recovery. Basic mechanisms of synaptic plasticity can be assumed to operate in stroke afflicted brains similar to those of the healthy brain (Felton et al., 2012). Neuroimaging studies using functional magnetic resonance imaging (fMRI) have shown exactly such

increased cortical activation in areas damaged by stroke following BCI therapy and training (Young et al., 2014a). Specifically, learning theories like Hebbian plasticity and conditioning may facilitate rehabilitation in stroke survivors by reinforcing existing functional connectivity necessary for producing sufficient cortical activity essential for smooth and controlled motor output (Bach-y-Rita, 1990; Biasiucci et al., 2018). This potential therapeutic mechanism of BCI may offer predictive indications about the relative likelihood of extinction or retention of the newly learned behavior and such pairing may also be measurable by observable changes in task-specific brain changes, like those described in this dissertation.

Evidence presented in Chapters 4 and 5 reinforce this assumption in this cohort while using this multimodal BCI-FES device. In a BCI paradigm, intrinsic rewards of success as well as extrinsic rewards of task completion or other afferent-based means of motor performance feedback (such as electrotactile or visual afference) are expected to guide behavior (Biasiucci et al., 2018) toward adaptive improvements in capacity and function. Furthermore, reward is important for motor reeducation and can integrate the reinforcement of functional and residual neural pathways (i.e., afferent monitoring of efferent motor plans) towards the successful completion of behavioral goals.

In addition to reward circuitry, it is thought that descending pathways controlling aspects of distal movement are benefited by the contingency of intent-to-move neural signals recorded by scalp EEG and the contingent muscle activation and associated afferent feedback of the FES adjuvant in this design. Noninvasive ‘hijacking’ of the brain’s residual functional connections by a BCI may be used to support the recovery of functional capacities in the brain such as voluntary motor function through such goal-directed practice and training as is evident in the cursor and target task. Pairing intent-to-move brain signals with stimulation of the distal hand muscles facilitates not only physical muscle contraction but also sends accompanying afferent signals back into the sensorimotor system, thereby closing the native feedback loop. BCI technology is well suited for neural rehabilitation poststroke as it utilizes the user’s direct neural input for the purpose of manipulating a peripheral component, such as a user’s hand, either via FES or other facilitating mechanisms (Simon et al., 2021) (Popovic et al., 2002c; Popovic et al.,

2004a; Popovic et al., 2004b; Pfurtscheller et al., 2005b; Birbaumer and Cohen, 2007; Shin et al., 2008; Page et al., 2009; Cho et al., 2011; Iftime-Nielsen et al., 2012; Colachis et al., 2018; Remsik et al., 2019). It is understood that the reward of these 'targeted activations' acts to improve the likelihood of functional cortical activation, BCI task completion, and subsequent reinforcement provided by the task's parameters (Young et al., 2015). Presumably, even in trials where little or no motion is realized or facilitated, individuals might experience recovery of functional cortical activity or augmentation of existing functionality, attributable to BCI system therapies.

In Chapter 5, evidence presented supports the theory that contingency-based brain changes localize to sensorimotor areas over the course of BCI intervention, and that these changes are adaptive and linked to behavioral improvements. These findings are also present when ERD is extrapolated from two-dimensional space to a three-dimensional realistic head model using the MNI152 template where cortical space is extrapolated to subcortical voxel space. Evidence supports ipsilesional primary motor area, premotor area, and supplementary motor area involvement in BCI-based plasticity changes resulting from multimodal BCI-FES use. Pre to Post intervention, participants also realized increases in functional connectivity intrahemispherically between the ipsilesional primary motor and premotor cortices in the Mu band. These findings highlight the significant contribution of intrahemispheric activity-dependent changes to subsequent behavioral improvements and are summarized in Figures 4 and 7 in Chapter 5. Evidence that neuroplastic changes are significantly correlated with improvements in hand grip strength, as measured by a dynamometer, further support the theory that brain signal changes localized to the ipsilesional motor areas are indicative of motor learning and can be measured as motor recovery.

The analysis in Chapter 5 of isolated effective coherence present additional evidence of contralesional, or interhemispheric contributions in brain changes associated with multimodal BCI-FES. In Figures 6 through 9 from Chapter 5, evidence supports the theory that, as a result of multimodal BCI-FES intervention, relative brain signal changes and measures of functional connectivity highlight the importance of ipsilesional brain areas, regardless of whether they are associated with changes that

originate intrahemispherically or interhemispherically. The changes evidenced in these figures highlight the existence and importance of functional connectivity changes to the rehabilitation of volitionally controlled motor output of the upper extremity, and they support the theory that neuroplastic mechanisms underlie the effectiveness of BCI-FES-based motor rehabilitation designs.

LIMITATIONS

While small-scale, observational findings in the use of BCIs for motor rehabilitation have highlighted the promise of this technology for stroke survivors, a standardized BCI-FES intervention schedule and dosing regimen has yet to be recognized for optimal treatment of hemiparesis (Remsik et al., 2016) (Bai et al., 2020) (Simon et al., 2021). Development of a standard rehabilitation protocol requires large cohort studies and increased monitoring in clinical settings beyond the laboratory.

Heterogeneity in intervention effects may be compounded by the limitations of any given outcome measure (i.e., sensitivity, suitability), and the large variability in location and extent of stroke-induced damage among survivors. As stroke may affect either multiple aspects of one's life, or a stereotyped movement (e.g., hand grasping), it is important to employ a diverse battery of neuropsychological assessments in order to capture any adaptive or maladaptive effects that may result from the intervention.

Design

Adjustments to various components of the BCI-FES intervention design (e.g., more intervention, more frequent intervention, etc.), display enrichment (e.g., enhanced gameplay and graphical presentation), or improvements in functional (i.e., task) relevance (e.g., simple instructed wrist supination and pronation, compared to pouring a virtual glass of liquid into another virtual glass etc.) might further facilitate motor recovery in stroke participants using a BCI-FES with multimodal feedback. Such enhancements to BCI intervention designs might improve participants' engagement, attention, and motivation during the intervention sessions, potentially increasing their neuroplastic affects (Seo et al., 2019). Participants might also benefit from increased monitoring of self-reported fatigue or motivation throughout the intervention sessions. BCI-FES is most effective when participants are actively engaged in

the task and, therefore, it may be important to measure changes in engagement due to fatigue, boredom, or other limitations, and lapses in concentration (Seo et al., 2019). Additional research on the effects of these and other considerations not raised here, may help to increase the effectiveness of BCI-FES interventions for upper extremity motor recovery in stroke survivors.

Control Features

Although the specific control features that are selected to trigger FES may vary from participant to participant, the common principle between participants is that the features selected derive from EEG frequency bands and cerebral cortical areas known to be associated with sensorimotor processing and voluntary motor output. Thus, the BCI device is adapted to each participant individually, which aids participants with different motor capacities and brain volumes to use the device (Bundy et al., 2012).

Dose

Data presented in other work from our laboratory (Young et al., 2014a) (Song et al., 2015b) (Young et al., 2015) (Young et al., 2016) (Mazrooyisebdani et al., 2018) (Mohanty et al., 2018) suggest that a dose of two-hour sessions for up to 30 hours with this BCI-FES intervention design is sufficient to positively effect motor recovery in stroke participants. Furthermore, a larger number of runs of this BCI-FES intervention results in greater brain and behavioral changes associated with recovery. Further research, specifically investigating how behavioral improvements depend on dosage categories (i.e., low, medium, or high) is needed to optimize dosage for specific individuals.

Supplemental Stimulation Adjuvants

Incorporating an adjuvant stimulus component (e.g., FES, TDU, haptic feedback, etc.) and multimodal feedback into the BCI intervention design may engender a more dynamic rehabilitative approach (Bach-y-Rita, 1990). Clinical fidelity is thought to depend largely on the sensory feedback that establishes the non-invasive closed-loop system (Biasiucci et al., 2018) (Simon et al., 2021). The feedback of the BCI-FES design can help shape the motor efference produced in cerebral cortical motor areas, and when this association remains consistent over time, the brain will adapt. The BCI-FES design presented here can drive that adaptation toward useful recovery of motor function. Inclusion of adjuvants

may also pose specific limitations, such as managing consistent placement of the FES electrodes across subjects, across sessions, as well as variations in sensitivity threshold and willingness of participants to receive adjuvants that deliver stimulation. The present BCI-FES design limits participants to simple whole hand flexion or extension of the fingers (i.e., repeated hand grasping) and some stroke survivors may benefit from practicing different or more complex movements, which the current BCI-FES configuration is not designed to support.

RECOMMENDATIONS

It will be important to understand the complex interactions between rehabilitation and a number of factors including lesion location, baseline motor capacity, the amount of BCI training, the type of neural activity used for BCI control, nature of BCI feedback, the latency between neural activity and external stimulation, and the combination of BCI training with any additional therapies to enhance plasticity and motor recovery. Through well-designed studies to determine the relative contribution of these factors, it will be possible to develop and translate BCI systems into clinical tools capable of driving lasting improvements to participant's physical capacity, independence, and quality of life.

In addition to considering device parameters and usage along with baseline and presenting biological factors of potential BCI users, it will be important to consider ancillary stroke-related-impairments that might impact a participant's recovery potential or ability to use the BCI device. For example, when considering who should get BCI or be included in BCI studies to identify various factors of BCI use and its clinical efficacy, special attention should be given to participants lacking motivation or desire to use a BCI, those with aphasia, impaired afferent systems (e.g., vision limitations, proprioceptive or cutaneous sensory loss) concentration limitations, and fatiguability.

Future research can build on these findings in a number of ways. First, results of BCI intervention in stroke survivors should be compared to individuals using a BCI that do not have presenting neural limitations or damage at baseline and those who have not had a stroke. Comparisons between "healthy normals" and stroke survivors will benefit from these groups being age matched as neural process and

capacities degrade with age, despite neuroplasticity being evident throughout the course of life for adult humans. Further research should seek to better account for individual differences when grouping participants for treatment type or intensity and such independent factors should be compared to BCI task performance averages as well. The analyses presented here are limited to two known frequency ranges associated with BCI control and adult human motor output: Mu and Beta frequency bands. While other brain frequency bins are known to be associated with various aspects of voluntary movement, such as theta and delta frequency ranges, they have not been considered in these analyses and no assumptions as to their relative contributions or importance are able to be made herein. However, it is entirely possible that there are clinically and scientifically meaningful associations to be discovered which may improve clinical efficacy or expand science's understanding of the neural mechanism impacting BCI-FES device or trial designs.

In this dissertation, evidence of plasticity is presented in general spatial terms, the specificity of which is limited by the inherent spatial acuity shortcomings of scalp recorded EEG and would benefit from more acute and precise measurements from techniques such as fMRI and DTI. For example, it is not currently feasible to test assumptions of the various neural circuits or pathways involved in the measured neural plasticity, or those that may underly measured behavioral gains. For example, it is not possible with the proposed measurement strategies to determine the relative contributions of lateral or medial descending motor systems to the behavioral improvements that were measured as a result of multimodal BCI-FES use in this current design. From the present data, it is possible to hypothesize which contributions might be associated with which pathways but more tightly constrained testing, using more sensitive neuroimaging measures is necessary to definitively answer research questions regarding the relative contribution of ipsilesional and contralesional pathways to motor recovery (Dodd et al., 2017). Further, such advanced techniques would also aid in the identification, beyond what is possible by the techniques used here, of the precise location and nature (i.e., reliability, acuity, specificity, etc.) of the intent-to-move brain signals used as inputs for this multimodal BCI-FES device.

It is recommended that future deigns more strictly consider the timing and contingency of delivered adjuvant stimulation and usefulness of reinforcement methods as well as the functional relevance of BCI-trained behaviors (e.g., wrist flexion or extension vs. wrist supplantation or pronation) relative to participant rehabilitation goals. In this design, the device is configured so as not to elicit FES stimulation beyond the period when the cursor or target is displayed on the screen, nor during unimpaired hand trials. In this way, FES is only delivered when the participant is generating intent-to-move brain signals associated with the impaired hand. Further, as illustrated in Chapters 4 and 5, there is no opportunity for the user to receive stimulation outside the temporal bounds of any one trial. This design does, however, leave opportunity for the participant to initiate intent-to-move signals when the target or cursor are not present, although all participants were observed to stop attempting hand movements immediately after the presentation of the target and cursor cue disappear and none were observed to initiate attempted hand movements during the intertrial interval.

The true contribution of FES is thought to provide more natural type of feedback to sensorimotor cortices and not the facilitated or supplemented stimulation of the motor axons. While the true advantage of the FES might not be in stimulating axons necessary for muscle contraction but rather facilitates the sensory contributions of movement expected in the full inverse model creating, as close to normal as possible, the inherent feedback loop of motor control. In terms of sensory feedback, the multimodal BCI-FES device as described herein has somatosensory, visual, and electrotactile feedback that are reinforcing one another and together, they might be more powerful than somatosensory feedback alone. These multimodal afferents are aligned, integrated in time, and understood to reinforce one another. Multimodal contingency is what generates the multimodality feedback inherent to the effectiveness of this system over other BCI designs (Simon et al., 2021) (Biasiucci et al., 2018).

By modifying various aspects of this device or trial design, it may be possible to enhance its effectiveness and usability for improved treatment of upper extremity hemiplegia resulting from stroke. First, as mentioned, a richer and more engaging task that has a higher degree of functional relevance to

the participant, (e.g., tasks within the capacity of the user to perform such as index to thumb pinch as compared to extension or flexion of the wrist) might result in more effortful participation as well as more meaningful and measurable changes in behavioral capacity. Also, a more standardized means for placing FES electrodes and EEG cap could help increase the fidelity between intent-to-move signals and facilitated activation of distal musculature. Other such improvements or changes to the design, parameters and use of this and like devices should be studied with the intent to improve clinical efficacy and quality of life for the stroke survivor.

SUMMARY

This dissertation presents device parameters and intervention protocols of this closed-loop, EEG-based BCI-FES system which, combined with standard physical rehabilitation approaches, has been validated and proven efficacious in the rehabilitation of upper extremity motor function poststroke in our ongoing cross-over controlled clinical trial (ClinicalTrials.gov study ID NCT02098265) (Young et al., 2014a) (Young et al., 2015) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021). This BCI-FES system elicits positive changes in the primary outcome measure (ARAT score: Arm Reach Action Test) (Lyle, 1981) as well as beneficial physiological changes in secondary outcome measures of neural activity (e.g., Mu ERD. The system's efficacy relies on specific targeting of neuromuscular activity contingent on intent-to-move neural signals, recorded with scalp electrodes overlying cerebral cortical sensorimotor areas, as well as concurrent delivery of multimodal sensory feedback through implementation of a chain of straightforward operating procedures. The scalp EEG signals provide an efficient and practical way to extract, in real-time, the relevant control features, and to deliver the desired feedback to the patients as part of an interactive and closed-loop neural activity-triggered application. We also present data from stroke survivors that demonstrate the utility of this BCI-FES design in rehabilitation for survivors at various levels of impairment and times since stroke. The present BCI-FES protocol, integrated with standard rehabilitation approaches, may provide a substantial improvement toward sensorimotor functional recovery of the impaired extremity in stroke survivors.

CONCLUSION

BCI-FES systems 1) have the potential to be significantly more cost-effective than traditional rehabilitations (i.e., naturally modifiable and can be configured to address individuals' needs or environmental constraints such as budget, space or location), 2) provide therapy that supplements, and potentially shortens or replaces conventional poststroke care, and 3) provides rehabilitative therapy that may be superior to present day standards of care, particularly in both the most severely impaired and chronic survivors of stroke. Primary outcome scores (e.g. Action Research Arm Test, Fugl-Meyer Test) following intervention suggest that the present BCI-FES design is able to deliver moderate improvements in UE motor function supported by evidence of similar improvements in several other subjective and objective measures of stroke impact (Song et al., 2014c) (Young et al., 2014c) (Young et al., 2014a) (Young et al., 2014b) (Song et al., 2015b) (Young et al., 2015) (Young et al., 2016) (Remsik et al., 2018) (Remsik et al., 2019) (Remsik et al., 2021).

The present non-invasive, EEG-based BCI-FES intervention has the potential to improve rehabilitation poststroke over and above the conventional standards of care in use at the present time. Each of the three example participants included herein demonstrated an increased capacity to perform the BCI-FES task accurately over the course of intervention. Although it may take time for a user to become proficient at the BCI-FES task requirements (i.e., volitional control of the cursor's movement across the screen), nearly all users who are able to understand the instructions are able to use and benefit from the technology. Whereas the features of rehabilitation might differ from person to person, the mechanisms of motor learning and brain-computer interfacing are ubiquitous as they rely on native CNS functioning which appears to be satisfactorily preserved in the poststroke brain. The BCI-FES concept is generalized across participants in that the means for using a BCI naturally exist in most all participants (e.g., even in the case of hemispherectomy) (Bundy et al., 2018), yet the application of the intervention may be personalized. Thus, the BCI-FES intervention presented here allows for clinical translation of BCI-FES technology in a manner that tailors the therapy to the needs and circumstances of specific individuals, thereby providing a basis for personalized, precision medicine.

BCI-FES designs are cost-effective and superior means of delivering poststroke care that are capable of supplementing or partially replacing traditional physical therapy regimens. The BCI-FES is a most promising design for the future of BCI-mediated rehabilitation of stroke (Simon et al., 2021). Further improvements in BCI design, such as updating to wireless communication between system components, decreasing system size and cost, as well as gamification and simplification of the user interface, and fidelity of therapeutic adjuvants, will further minimize costly healthcare supervision and, therefore, will increasingly satisfy requirements of healthcare payers for more cost-effective means to supplement and enhance conventional physical therapy for stroke survivors within and beyond traditional care windows. The closed-loop nature of this BCI-FES design enhances experience-dependent neuroplasticity (Bach-y-Rita, 1981) (Bach-y-Rita, 1990) (Nudo, 2003b) (Wolpaw, 2012), especially in the sensorimotor system, driving neurophysiological changes that promote functional recovery of stroke-impaired UE, regardless of other factors. In this BCI-FES intervention design, FES of the stroke impaired muscles contingent on participant-generated control features in the recorded EEG signals associated with movement intent elicits subsequent signaling in multiple native sensory (cutaneous, proprioceptive, visuo-motor, etc.) and motor circuits that likely enhance and refine subsequent intent-to-move signals (i.e., motor command signals) and efficacy of subsequent motor behavior.

Chapter 7
Conclusion

This dissertation provides evidence of efficacy and therapeutic mechanisms of action for multimodal BCI-FES in the treatment of upper extremity hemiplegia resulting from stroke. Despite clinical and scientific efforts to improve standards of poststroke care, most stroke survivors suffer some level of persistent upper extremity impairment. BCI technology provides patients a volitionally controlled plasticity-based neurorehabilitation regimen designed to leverage functional connectivity to drive motor learning and recovery.

While the majority (64%) of participants with room for improvement realized beneficial gains in physical motor capacity, as measured by the Action Research Arm Test (ARAT), statistically significant improvements were consistently measured across participants in standardized self-report measures of motor function following intervention. It is possible that the significant changes in task-specific brain activity and functional connectivity that correlate with behavioral gains resulting from multimodal BCI-FES, while meaningful to the participants' activities of daily living, do not result in clinically meaningful or significant behavioral increases across all participants. Therefore, it's clear that continued research efforts, specifically, into the mechanisms behind functional connectivity and its relationship to behavioral recovery and behavioral change require further investigation. Future studies must address these issues with neuroimaging methods of high spatial acuity, and in cortical and sub-cortical space.

In addition to providing improved care for stroke survivors beyond traditional care windows, BCI-FES represent a solid scientific tool for studying the neural mechanisms of motor learning and recovery more broadly. The methods presented in this dissertation represent the best or nearly the best possible tools available to testing these research questions and acquiring these data in an ethical, humane, compassionate, just, and minimally invasive way.

It is essential to continue research and development of BCI-FES devices for the purpose of improving quality of life and autonomy for stroke survivors in their daily living activities. Ultimately, these research questions and efforts are worth pursuing for the betterment of stroke survivors and their quality of life, as well as the advancement of understanding and knowledge in science and this dissertation represents a meaningful step towards clinical translation of a standardized design for BCI-FES interventions to those ends.

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