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Controlling Pre-Movement Sensorimotor Rhythm Can Improve Finger Extension after Stroke

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ABSTRACT

Objective. Brain-computer interface (BCI) technology is attracting increasing interest as a tool for enhancing recovery of motor function after stroke, yet the optimal way to apply this technology is unknown. Here, we studied the immediate and therapeutic effects of BCI-based training to control pre-movement sensorimotor rhythm (SMR) amplitude on robot-assisted finger extension in people with stroke.

Approach. Eight people with moderate to severe hand impairment due to chronic stroke completed a 4-week 3-phase protocol during which they practiced finger extension with assistance from the FINGER robotic exoskeleton. In Phase 1, we identified spatiospectral SMR features for each person that correlated with the intent to extend the index and/or middle finger(s). In Phase 2, the participants learned to increase or decrease SMR features given visual feedback, without movement. In Phase 3, the participants were cued to increase or decrease their SMR features, and when successful, were then cued to immediately attempt to extend the finger(s) with robot assistance.

Main Results. Of the four participants that achieved SMR control in Phase 2, three initiated finger extensions with a reduced reaction time after decreasing (vs. increasing) pre-movement SMR amplitude during Phase 3. Two also extended at least one of their fingers more forcefully after decreasing pre-movement SMR amplitude. Hand function, measured by the Box & Block Test (BBT), improved by 7.3 +/- 7.5 blocks vs. 3.5 +/- 3.1 blocks in those with and without SMR control, respectively. Higher BBT scores at baseline correlated with a larger change in BBT score.

Significance. These results suggest that learning to control person-specific pre-movement SMR features associated with finger extension can improve finger extension ability after stroke for some individuals. These results merit further investigation in a rehabilitation context.

INTRODUCTION

Stroke is the leading cause of severe movement disability worldwide (Lopez, Mathers et al. 2006, Feigin, Forouzanfar et al. 2014); it affects more than 700,000 people in the US each year (Broderick, Brott et al. 1998). Approximately 82% of people with acute stroke experience motor deficits, with about 76% experiencing upper extremity deficits (Rathore, Hinn et al. 2002). To reduce motor impairment, people with stroke typically undergo several months of movement rehabilitation therapy; this is associated with inconsistent and often modest benefits. An important direction for stroke rehabilitation research is to

develop training techniques that best engage the resources for neuroplasticity that each patient retains after stroke (Boyd, Hayward et al. 2017).

Robotic devices, including exoskeletons, have been developed to assist movement training for people with stroke and other neurologic impairments (Reinkensmeyer, Emken et al. 2004). Developers typically state three main goals for such devices: automating the repetitive and strenuous aspects of movement training; delivering rehabilitation therapy in a more repeatable manner; and quantifying outcomes with greater precision. In addition, robotic assistance can enhance afferent feedback, which may aid in neural reorganization (Takahashi, Der-Yeghiaian et al. 2008, Hornby, Reinkensmeyer et al. 2010, Rowe, Chan et al. 2017). Systematic reviews indicate that well-designed robot-assisted therapy typically produces results equal to or slightly better than the results of conventional rehabilitation techniques (Kwakkel, Kollen et al. 2008, Mehrholz, Platz et al. 2008). Nevertheless, the benefits are modest, and an important direction in robot-assisted training is to develop novel approaches that increase benefit, as well as to accurately identify individuals who can benefit from specific approaches.

Brain-computer interface (BCI) systems have been proposed in this regard; they are attracting increasing interest to enhance rehabilitation protocols in people with motor impairment after a neurological injury (Daly and Wolpaw 2008, Ang and Guan 2013, McCrimmon, Wang et al. 2016). The most common use of BCI for movement rehabilitation employs muscle stimulation or orthotic assistance that is contingent on the subject generating a target pattern of brain activity. This approach might augment movement recovery by using operant conditioning to normalize brain states conducive to movement, or by coupling movement-related brain states to time-correlated sensory feedback (Daly and Wolpaw 2008, Cramer, Sur et al. 2011, Ang and Guan 2013).

One brain signal often used in BCI applications is the sensorimotor rhythm (SMR). SMRs are 8-12 Hz or 18-26 Hz rhythms in electroencephalographic (EEG) activity recorded over sensorimotor cortex (Pfurtscheller and McFarland 2012). SMR decrease, called event-related desynchronization (ERD) (Pfurtscheller and Aranibar 1977, Pfurtscheller and Lopes da Silva 1999) typically occurs before and during active movements; SMR increase, called event-related synchronization (ERS), typically occurs after movement (Pfurtscheller and Aranibar 1977, Pfurtscheller, Neuper et al. 2005, Pfurtscheller and McFarland 2012). However, the neural mechanisms generating SMRs and how pre-movement SMRs affect subsequent motor behavior are less clear. SMR changes appear to result from a distributed process including premotor and motor cortices, subcortical, and spinal centers (Cohen, Sherman et al. 2010). High SMR power at rest is thought to reflect motor inhibition (Pfurtscheller 1992), a view consistent with SMR ERD before and during movement and SMR ERS after movement. On the other hand, SMR changes are not linked solely to active movement; they may also change in response to afferent input alone, as evidenced by their modulation prior to passive movements produced by a robotic orthosis (Formaggio, Storti et al. 2013, Norman, Dennison et al. 2016). Taken together, this evidence suggests that control of SMR may play a role in movement control and learning by altering motor excitability and/or modulating afferent input.

Several studies have explored SMR training as an intervention for people with motor deficits after stroke (Buch, Weber et al. 2008, Daly, Cheng et al. 2009, Broetz, Braun et al. 2010, Prasad, Herman et al. 2010, Ramos-Murguialday, Schurholz et al. 2012, Takahashi, Takeda et al. 2012, Ramos-Murguialday, Broetz et al. 2013, Pichiorri, Morone et al. 2015). Typically, these studies have focused on training SMR modulation during movement or movement imagery: they have used SMR amplitude to control robotic orthoses that assisted movement, or they have sought to improve SMR ERD during movement with the expectation that this will improve movement. These studies assume that the temporal relation in activation of motor areas

and sensory areas associated with proprioceptive and tactile feedback produced by limb movement are beneficial to motor learning and rehabilitation, perhaps driven by Hebbian learning effects (Gomez-Rodriguez, Peters et al. 2011) or priming of subsequent physiotherapy (Curado, Cossio et al. 2015). In general, these types of BCI interventions have shown moderate clinical effects in controlled clinical trials (Cervera, Soekadar et al. 2017).

To the extent that poor motor preparation can also limit subsequent motor function, training pre-movement SMR control might also improve the ensuing motor action. In a BCI-motor task, McFarland et al. taught eight unimpaired people to regulate SMR amplitude before movement to initiate a subsequent upper extremity movement task. Following successful BCI training, 3 of 8 participants significantly reduced response times when they reduced SMR amplitude before movement (McFarland, Sarnacki et al. 2015). Delays in movement initiation have been described in finger extension after stroke (Seo, Rymer et al. 2009). These delays limit motor function and contribute to disability in hemiparetic patients (Chae, Yang et al. 2002), suggesting them as possible targets for intervention. Another benefit of training pre-movement SMR regulation is that it may better prepare sensorimotor cortical areas vital to motor learning after stroke. In unimpaired people, down-regulating SMR naturally occurs before movement onset and is likely related to the generation and processing of afferent information that can drive motor learning (Formaggio, Storti et al. 2013, Norman, McFarland et al. 2016). However, pre-movement SMR changes are attenuated in people with motor impairments (Fu, Daly et al. 2006). Here, we train pre-movement SMR control online for the first time in people with stroke.

In this study, we hypothesized that: 1) people with stroke can learn to control SMR amplitude; and 2) pre-movement SMR amplitude modulation will affect movement onset latency and maximum finger extension torque. We also quantified the functional impact of this training, which would presumably be due to motor learning, using a standard clinical measure of hand function.

This study differs from previous efforts to apply BCI technology in rehabilitation in that it uses the BCI to improve preparation for movement rather than using the BCI to assist movement or to modify the brain state during movement. This approach relies on evidence that advanced preparation improves subsequent motor performance and the assumption that improved performance can result in a therapeutic benefit. Elevated motor cortical power has been shown to be associated with neural patterns that promote tone and slow movements (Gilbertson, Lalo et al. 2005). Later studies exploited this association in non-human primates (Khanna and Carmena 2017) and humans (Boulay, Sarnacki et al. 2011, McFarland, Sarnacki et al. 2015), showing that reducing motor cortical power can reduce subsequent movement onset delay. Although therapeutic mechanisms are less well defined, controlling SMR into a movement-favorable state before moving may allow individuals to repeatedly practice better quality movements with improved motor cortex excitability (Pichiorri, De Vico Fallani et al. 2011), which may be beneficial for motor learning and rehabilitation (Stinear, Barber et al. 2008, Pomeroy, Aglioti et al. 2011, Stinear, Petoe et al. 2014, Hsieh, Wu et al. 2017).

This study is unique also in that it used a finger-individuated robotic hand orthosis. This permitted training more complex movement tasks (e.g. extending one finger while inhibiting movement in another – i.e. finger individuation), which are tasks with greater cognitive requirements since they involve more complex decision making based on cues. Specifically, we employed a visual matching task that asked the participant to identify spatially distributed stimuli and then make the appropriate finger movements or non-movements. Such complex tasks can increase activity in brain motor areas more than simpler tasks (Meister, Krings et al. 2005). Furthermore, complex action selection matching tasks may improve motor

training for people with chronic hemiparesis after stroke (Stewart, Dewanjee et al. 2016). Finally, this study focused on finger extension movements, because extension movement onset (Seo, Rymer et al. 2009) and torque production are particularly impaired in people with stroke, thereby limiting overall hand function (Conrad and Kamper 2012, Wolbrecht, Rowe et al. 2018).

METHODS

Participants

We recruited individuals who: had experienced a single hemorrhagic or ischemic stroke at least six months previously that had spared the ipsilesional precentral gyrus (i.e., the stroke was subcortical or, if it was cortical, it spared the primary motor area); and had a significant but not total deficit of finger motor function, defined as a Box & Block Test (BBT) score from 1-25 (i.e., less than one-third normal, but able to manipulate at least one block). The resulting eight (N=8) participants were all men, aged 44-83 (mean 59.5 +/- SD 11.8), with BBT score at baseline from 1-28 (mean 12.0 +/- 8.5), and arm motor Fugl-Meyer Assessment scores at baseline of 23-50 out of 66 (mean 37.6 +/-11.0). All participants were new to BCI training and achieved a satisfactory score (minimum 24) on the Montreal Cognitive Assessment (MoCA). All participants provided written informed consent and the study was approved by the Institutional Review Board of UC Irvine. The authors have confirmed that any identifiable participants in this study have given their consent for publication.

Protocol

Each participant completed a four-week, 12-session protocol (3 sessions/wk). Each session comprised eight 3-min runs of about 30 trials each, for an average total of 240 trials/session. The study was divided into three phases. Phases 1 and 3 each lasted one week, and incorporated finger extension practice using the Finger Individuating Grasp Exercise Robot (FINGER) robotic exoskeleton (Taheri, Rowe et al. 2014). Phase 2 lasted two weeks and focused solely on SMR control (Fig. 1). Phase 1 identified 1-3 SMR features in the EEG during preparation for finger extension that correlated with the Go/NoGo condition of the finger extension movement trial. Phase 2 trained users to increase or decrease the amplitude of these SMR features using visual feedback only, without attempting to move the fingers. Phase 3 combined the SMR regulation of Phase 2 with the movement of Phase 1 to evaluate the effects of pre-movement SMR amplitude control on an immediately ensuing finger extension movement attempt.

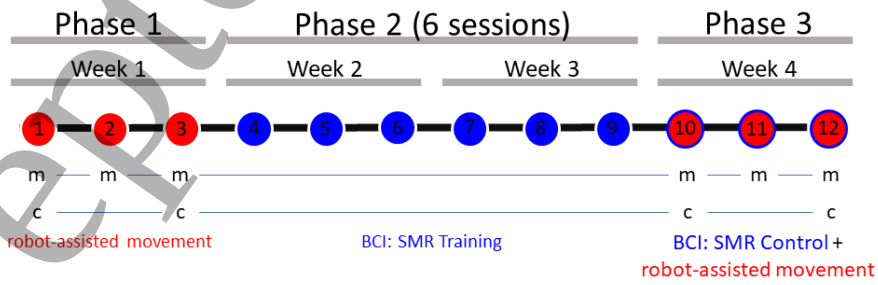

Figure 1: Timeline of study. Each dot represents a day with one session of training. Each group of three dots represents one week of training (4 weeks total). Red dots are robot-assisted movement sessions; blue dots are BCI-based SMR/visual feedback-only sessions; blue/red dots are sessions in which SMR control triggered robot-assisted movement. Phases 1 and 3 had three sessions each, while phase 2 had six

sessions. Movement (finger extension) analyses are indicated (m). Clinical assessments (c) of upper-extremity movement ability (Box & Block) were conducted at the beginning and end of phases 1 and 3.

Phase 1 – Identification of SMR features

In Phase 1, we sought to identify participant-specific SMR features that predicted the intent to try to extend the fingers as quickly and forcefully as possible. Participants sat in a chair facing a 24" 1920x1080 monitor placed on a table 1.5 m away while EEG was recorded. Participants completed a Go/NoGo task cued on the monitor. "Go" trials required them to extend the index finger only, the middle finger only, or both fingers together. On these trials, robot assistance was provided by the FINGER robot (Taheri, Rowe et al. 2012). FINGER assisted flexion/extension of the index and middle fingers along a naturalistic grasping/release trajectory; it also recorded position, acceleration, and force at the proximal and middle phalanxes of the index and middle fingers to calculate torque at the metacarpophalangeal (MCP) joint. Robot data were sampled at 1000 Hz for the control loop and sub-sampled for recording at 64 Hz. On the "Go" trials, the robot did not assist until the participant reached a finger extension torque threshold equal to ~0.034 Nm. This required the participant to initiate each trial; once this occurred, the robot-assisted for the remainder of the movement. This assistance enabled the participant to complete finger extension movements that he might not be able to complete on his own. Assistance torque was provided by a proportional-derivative position controller that corrected user movement towards a minimum-jerk trajectory that would complete a full extension movement in 0.5 s. Thus, if the participant lagged the trajectory, the robot would assist. However, if the participant exceeded the trajectory, the robot would slow the movement. We did not observe a slowing effect in any of the participants in this study.

Participants were visually cued to attempt different finger extension movements, which were randomized between 1) no movement (i.e. "NoGo" condition for both fingers); 2) move index finger only; 3) move middle finger only; and 4) move both fingers. All movements were attempted using the paretic hand. Each trial began with the fingers at rest in the flexed position. During a 1-s pre-movement period (Fig. 2a), the participant saw a yellow circle(s) for the to-be-extended finger(s) and a blue circle(s) for finger(s) that were to remain flexed. At the beginning of the subsequent response interval (Fig. 2b), yellow circles changed to green to cue extension ("Go" condition) and blue circles changed to red to cue the finger to remain flexed ("NoGo" condition for that finger). The participant was instructed to respond as quickly as possible to this imperative stimulus and had 2 s to complete the response. The participant's correct response to a "Go" cue elicited robot assistance for the remainder of the movement and the green circle grew in proportion to finger position as a form of positive visual feedback (Fig. 2c). If the response was correct and the movement was completed, the circle turned white for 1 s (Fig. 2d) and the participant was given visual feedback in the form of a score number indicating the latency from the go cue to finger movement initiation. If both fingers were given "NoGo" cues and the participants correctly remained at rest for 1 s, the circles turned white for 1 s. If the response was not correct, or 2 s expired, the screen went blank for 1 s. Fig. 2 also shows an example of the finger position response profile recorded from a single trial. After each movement, the robot returned the fingers to the flexed position and kept them there.

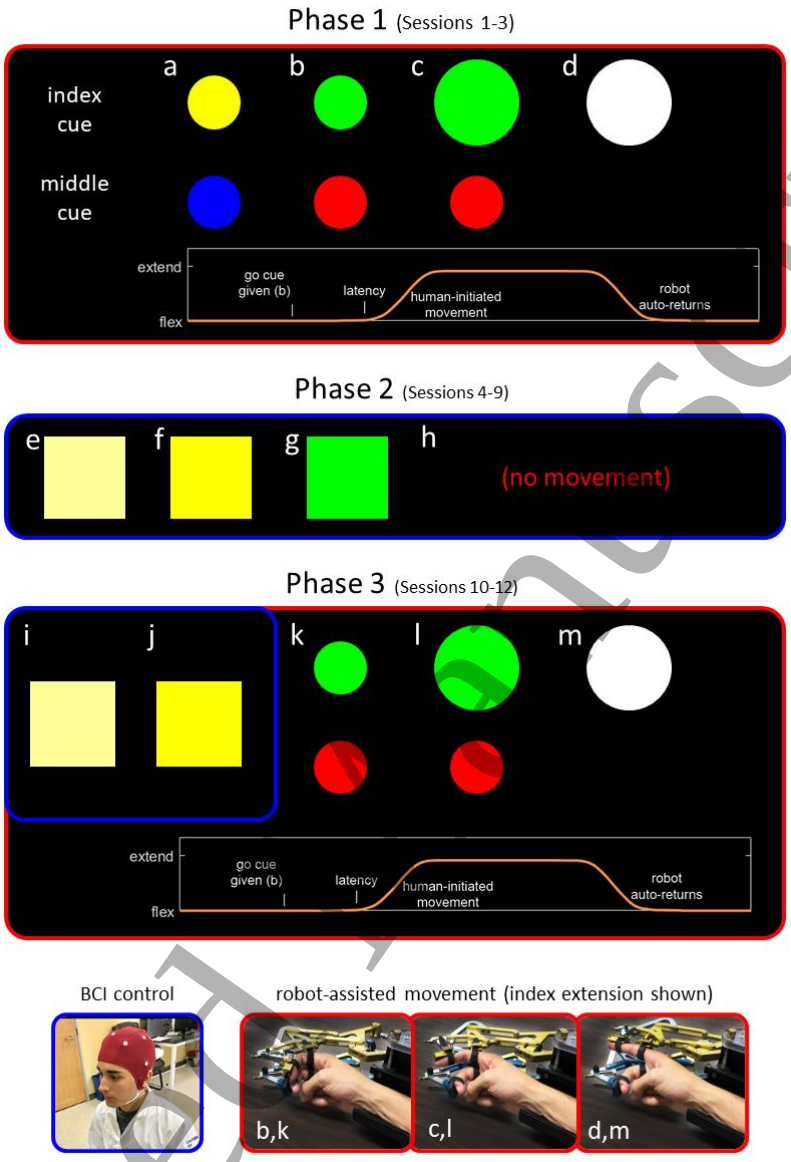

Figure 2: Trial progressions are shown for phases 1-3. BCI control components are in boxes outlined in blue; robot-assisted movements are in boxes outlined in red. Phase 1: Participants are cued to attempt extension of the index finger, middle finger, or both. Shown here are the visual cues for an index finger trial. (a); an index movement preparation warning cue (yellow dot); (b): the imperative "Go" cue for an index finger movement (green dot); (c): the participant's correct response (index finger extension) elicits robot assistance for the remainder of the movement and visual feedback occurs (green dot grows with finger position); (d): the dot turns white indicating a properly executed movement. Phase 2: The participant attempts to increase SMR amplitude for targets of one color (yellow or blue) and decrease SMR amplitude for targets of the other color. (e): a yellow square appears, prompting this participant to increase SMR amplitude (a blue square would prompt SMR decrease in this participant); (f) the square brightens as SMR amplitude approaches the criterion; (g) satisfying the criterion for 1 s produces a green square indicating success; (h) the screen goes blank for 2.5 s. Phase 3: (i): as in Phase 2, this participant modulates SMR amplitude; (j) as SMR amplitude approaches and satisfies the criterion value, the square brightens; (k)

when the SMR criterion is satisfied for the required 1 s, a movement stimulus appears; (l) the green circle grows with finger extension; (m) if the movement is properly executed, the green circle turns white; the screen is blank for 2.5 s and the robot returns the participant's finger to the starting position.

EEG data collection and processing

We recorded EEG with 9-mm tin electrodes embedded in a cap (Electro-Cap International, Inc.) at 16 scalp locations according to the modified 10-20 system of Sharbrough et al. (Sharbrough, Chatrian et al. 1991) (locations F3, Fz, F4, T7, C3, Cz, C4, T8, CP3, CP4, P3, Pz, P4, PO7, PO8, Oz). The electrodes were referenced to the mastoid and re-referenced in a bi-polar montage to Cz. The signals were amplified and digitized at 256 Hz by a g.tec g.USBamp biosignal amplifier. BCI operation and data collection were supported by the BCI2000 platform (Schalk, McFarland et al. 2004, Mellinger and Schalk 2009). We performed spectral analyses using the 24th-order autoregressive (AR) algorithm described in McFarland and Wolpaw (McFarland and Wolpaw 2008), similar to the 16th-order model used in (McFarland, Sarnacki et al. 2015). We used an increased model order due to the higher sampling rate (256 Hz vs. 160 Hz). This AR analysis determines the amplitude, i.e. square root of power, within discrete 3-Hz spectral bands from 12 to 24 Hz for 400 ms sliding windows updated every 50 ms for the one second after the warning stimulus (Fig. 2a) and preceding the imperative ("Go" or "NoGo") stimulus (Fig. 2b). In summary, the AR spectral analysis is a linear prediction filter that uses the Berg algorithm (Marple 1987) to estimate AR filter weights without necessitating matrix inversion. To estimate these weights and the resulting power spectra we used routines from (Press, Flannery et al. 1986). We chose these parameters, e.g. spectral bandwidth, and routines, e.g. Berg algorithm, to match our previous work and historical data in unimpaired people to avoid confounding comparisons.

EEG data modeling

We analyzed spatiospectral EEG activity from phase 1 for the immediate pre-movement period (i.e., between the warning and imperative cues) to identify the SMR features (i.e., amplitudes in specific frequency bands at specific locations over sensorimotor cortex of either hemisphere) that best predicted movement (of one or both fingers) vs. no movement. We used the Elastic Net with l_1 and l_2 regularization regression model in the glmnet package from R (Friedman, Hastie et al. 2010) to correlate potential SMR features (e.g., SMR amplitude at 12-15 Hz for electrode *C3*) with the warning cue value ("Go" vs. "NoGo"). We chose to use Elastic Net regression because, for people with stroke practicing robot-assisted finger movement, it generalized to new data with the highest accuracy among several regression models (Norman, McFarland et al. 2016). The elastic net minimizes the vector of regression weights:

$$\beta' = \operatorname{argmin}\{\sum(yi - \beta_0 - x_i{}^T\beta)^2 + \lambda P_\alpha\beta\} \quad 1)$$

where y_i is the *ith* value of the vector of values to be predicted, x_i is the *ith* vector of predictors, λ is the weight of the penalty term and:

$$P_\alpha(\beta) = \sum\{{}^1\!/_2\,(1-\alpha)\beta_j{}^2 + \alpha|\beta_j|\} \quad 2)$$

The parameters λ and α are optimized by a grid search of values determined by a glmnet package heuristic. A 7-fold cross-validation was performed using training data chosen at random from each participant's data from phase 1. This provides an optimized combination of *l1* (i.e., absolute sum of the weights) and *l2* (i.e., squared sum of the weights) penalties on the regression weights. The resulting EEG

features achieving the largest r^2 values were then used as the SMR features for online feedback in Phases 2 and 3.

Phase 2 – Sensorimotor rhythm training

In Phase 2, participants were trained to control the SMR feature amplitudes selected based on the analysis of the Phase-1 data. Each participant completed three sessions of Phase-2 training/wk for two weeks (6 total sessions). Each session lasted ~1 hr and included eight 3-min runs of SMR training. Participants learned to change (increase or decrease) the amplitude of the SMR feature(s) identified in Phase 1 using visual feedback in the form of color change of a square on the monitor. We suggested that they explore different motor imagery scenarios (e.g., finger movement vs. no movement) until they found a strategy that allowed them to control the BCI. For each trial, the starting color of the 5.1-cm square was randomly chosen to be yellow or blue. When the square appeared (Fig. 2e), the participants controlled the saturation of the colored square based on real-time feedback of their SMR amplitude. For squares of one color (yellow or blue), a given participant was asked to maintain the SMR amplitude above a criterion value for 1 s. For squares of the other color, the participant was asked to maintain the SMR amplitude below a criterion value for 1 s. The square became brighter as SMR amplitude approached the criterion for 1.0 s (Fig. 2f); when it satisfied the criterion for 1.0 s, the square became bright green for 0.5 s (Fig. 2g). A coding error resulted in three participants' (e,f, and h) mappings of SMR up-regulation vs. down-regulation to blue vs. yellow cues to be reversed. However, participants' mappings were maintained throughout phases 2 and 3; thus, besides the color reversal, this change did not affect the methodology or results. If SMR amplitude changed in the wrong direction (incorrect trial) or did not maintain the criterion for 1 s within 5 s (aborted trial), the screen simply went blank. After the completion of a trial, the screen remained blank for the 2.5-s inter-trial interval.

As described above, the specific spatiospectral features of the SMR were participant-dependent as determined from their Phase-1 data. We selected the SMR features that maximized the predictive movement/no-movement capacity for each participant.

Phase 3 – SMR-triggered movement performance

Phase 3 comprised three sessions over one week immediately following the conclusion of Phase 2. During Phase 3, participants were given visual feedback on their ability to change SMR amplitude. As during Phase 2, they were initially presented with a colored square that was color-saturated by correct SMR amplitude change. When the participant satisfied the criterion for 1 s, a movement trial was immediately cued. As in Phase 1, they were instructed to respond as quickly as possible to the cue. As in Phase 1, the robot actively maintained a constant position, thereby resisting movement and enabling isometric torque to be measured. Once the participants initiated a movement (i.e. reached the small torque threshold of 0.034 Nm), robot assistance was activated, extending the finger and thereby providing haptic feedback. Figure 2 shows a representative Phase-3 trial.

During Phase 3, we collected two primary measures of movement performance: latency to movement onset and maximum MCP torque. Latency to movement onset was defined as the time it took the participants to initiate movement (i.e., exceed the torque threshold that triggered robot assistance) after being given the "Go" cue. Torque about the metacarpophalangeal joint (MCP torque) was calculated based on the forces measured by transducers on the proximal and middle finger joints of the index and middle fingers. Here, we report peak MCP torque, calculated as the maximum MCP torque on an individual trial in the extension direction, normalized to the maximum torque across all phase 3 trials for that participant. Thus, MCP torque is reported as a value between 0 and 1.

Clinical Outcome

The clinical outcome measure of this study was the Box & Blocks Test (BBT) (Radomski and Latham 2008), in which a wooden box with two separate compartments divided by a partition is placed in front of the participant. The person then attempts to move as many one-inch cubic blocks as possible from one compartment over the partition into the other compartment in one minute. The average score for an unimpaired male age 60-64 is 71.3 +/- 8.8 blocks (Mathiowetz, Volland et al. 1985).

RESULTS

Phase 1 – Identification of SMR features

Phase-1 data were collected to identify participant-specific SMR features that best predicted the movement intention of the participant (i.e., whether they intended to move - to extend one or both fingers - or to not move). We successfully generated models for all eight participants that correlated SMR features with the Go/NoGo response condition in the training data from the first two sessions (R values were 0.18-0.78, mean R=0.53, $p<0.05$ for 8/8 participants and $p<0.01$ for 7/8 participants). These models generalized well to test data acquired from the third session (R values 0.078-0.77, mean R=0.48, $p<0.05$ for 7/8 participants and $p<0.01$ for 5/8 participants). For each participant, we selected the model that had the highest correlation to the response condition (i.e., Go or NoGo). The linear combination of these SMR features comprised the 'SMR Composite' signal that was used in Phase 2 to measure SMR amplitude. In other words, changing the SMR composite score –a linear combination of the power of the SMR features identified for each person – directly affected the stimulus color during Phases 2 and 3. Table 1 shows, for each participant, the 1-3 SMR features that had the largest weights in the regression models and thus were used to determine SMR amplitude. Note that all channels were bipolar referenced to Cz.

Phase 2 – Sensorimotor rhythm training

Table 1: The selected SMR feature(s) and final Phase 2 (session 9) BCI accuracy for each participant. Each frequency or band of frequencies, paired with the specified electrode, corresponds to a feature. Frequencies are reported as center frequencies of 3 Hz bands.

Subject	Impaired	Channel	Frequency (Hz)	Channel	Frequency (Hz)	Channel	Frequency (Hz)	Trials (correct/total)
A	R	C3	18, 24	C4	18, 21, 24	CP4	12, 24	143/172, **83.1%**
B	R	C3	21	C4	12, 21	-	-	116/152, **76.3%**
C	L	C3	21	C4	12, 21	-	-	077/105, **73.3%**
D	R	C3	15, 18	C4	18, 21	CP3	18	088/129, **68.2%**
E	R	CP3	18	-	-	-	-	093/125, **74.5%**
F	L	CP3	18, 21, 24	CP4	12, 24	-	-	147/170, **86.5%**
G	L	C4	12, 15	CP3	12	CP4	18	069/144, 47.9%
H	R	C3	21	CP3	12, 21, 24	CP4	12, 21	054/135, 40.0%

The purpose of Phase 2 was for the participants to learn through visual feedback to modulate the SMR amplitude selected for them in Phase 1 (Fig. 2). Table 1 shows the percentage of trials in the final Phase-2 session in which each participant modulated SMR amplitude appropriately. Aborted trials, i.e. those in which SMR amplitude did not reach the up criterion or the down criterion within 5 s, are excluded (abort rates ranged from 29-47%, mean 39%). To determine if the participants were controlling the BCI above chance level, we used the binomial distribution with a chance level of 0.50 and a threshold of $p<0.001$

(Combrisson and Jerbi 2015). Six of the eight participants achieved hit rates that were significantly above chance level (bolded in Table 1).

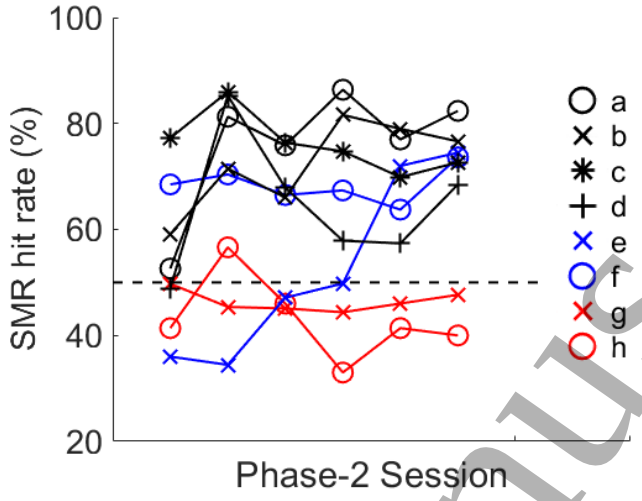

Figure 3: BCI hit rates across the Phase-2 sessions for each participant. Chance accuracy is 50% (dotted line). Four participants (a, b, c, d, in black) learned to control SMR amplitude. Two participants (e and f, in blue) exhibited broad spatiospectral patterns (see Fig. 4) indicative of control by head/neck muscle activity rather than actual SMR amplitude modulation. Two participants (g and h) did not gain control.

Topographical and spectral analyses provide important insight into each participant's control. Figure 4 shows for each participant the scalp topography and frequency spectrum for each participant for one of his selected SMR features (i.e., Table 1). The topography shows the scalp distribution of control (i.e., correlation with whether the instruction was to increase or decrease SMR amplitude) at the frequency of that feature; the spectra indicate the frequency-specificity of that control. Four participants (a, b, c, d) gained control that was focused in an SMR frequency band and concentrated over lateral or central sensorimotor cortical areas. Two participants (g, h) did not gain control. In the remaining two (e, f), the control was not spectrally or topographically focused; it extended across the frequency spectrum, indicating that it was almost certainly due to head/neck muscle activity (Goncharova, McFarland et al. 2003). In fact, the study proctors noted that these two participants (e and f) shrugged their shoulders or tensed their necks during recording sessions, despite requests to avoid doing so. Thus, these two participants did not demonstrate actual SMR control.

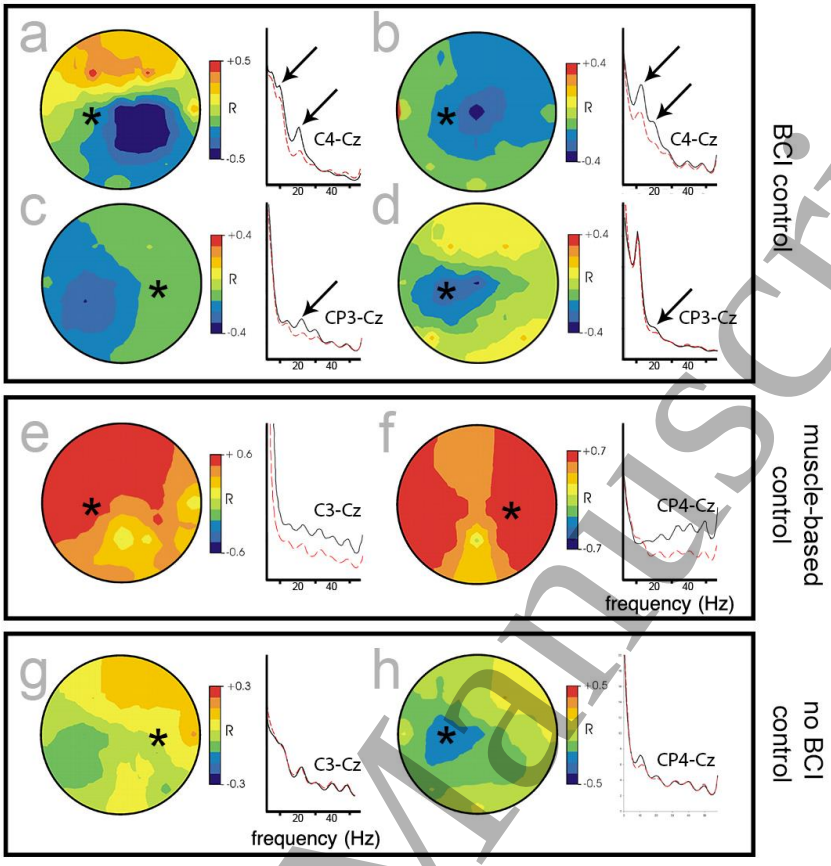

Figure 4: Topographies and spectra of the correlation (R-value) between the SMR feature amplitude and the target condition, SMR down-regulation (red) vs. SMR up-regulation (black). Data from the last phase-2 session are shown for each participant, a through h. Topographies and power spectra were generated using a bipolar reference to channel Cz; the specific channel used to generate the spectra for each participant is indicated. Asterisks denote the stroke-affected hemisphere. Participants a, b, c, and d exhibited narrow-band BCI control (arrows). Participants e and f showed broad-band control indicative of artifactual (i.e., probably head/neck muscle) activity. Participants g and h did not show significant control, although participant h did produce a narrow-band differential signal.

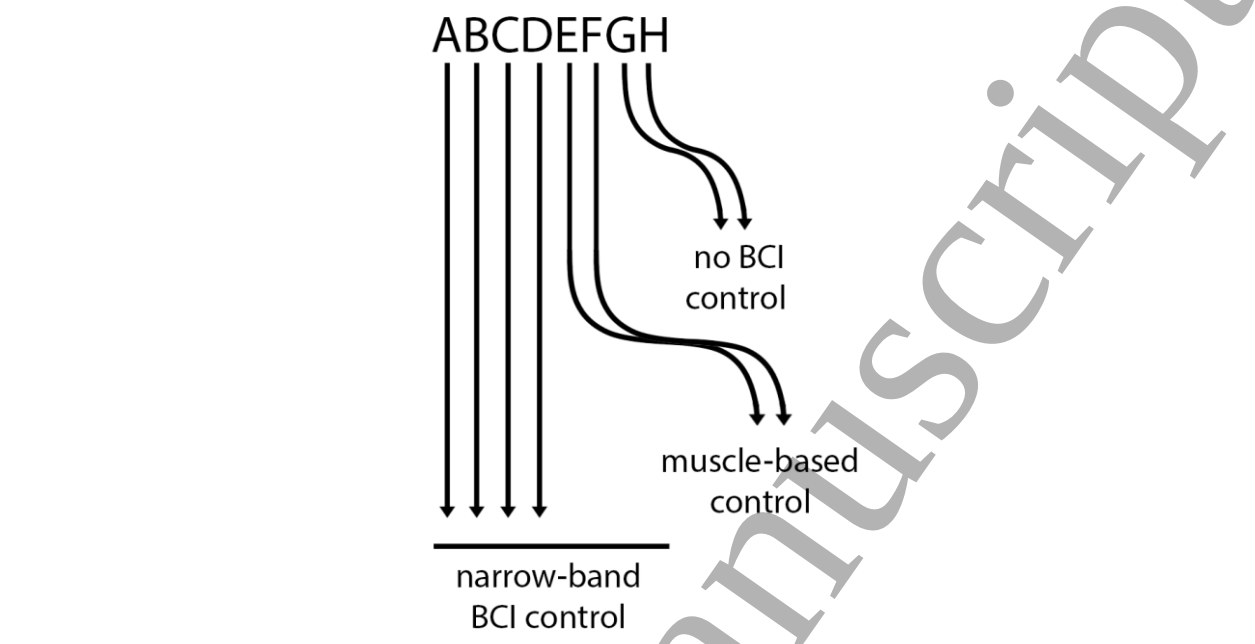

Figure 5: Participants a, b, c, and d exhibited narrow-band BCI control above chance level. Participants e and f exhibited broad-band artifactual (i.e., head/neck muscle-based) control. Participants g and h did not achieve control. Thus, further analyses of the effects of BCI training on motor performance excluded participants e-h.

The purpose of Phase 3 was to combine the SMR feature modulation of Phase 2 with the overt movement of Phase 1 to explore the impact of pre-movement SMR modulation on subsequent movement performance in people with stroke. In Phase 3 as in Phase 2, the participants modulated SMR amplitude up or down as instructed on the monitor. Once they had maintained the SMR criterion value for 1 s., a finger extension task was immediately cued (Fig. 3k). We quantified two movement performance measures: latency to movement onset and maximum extension torque at the MCP joint. We focus our analysis here to the four participants (a, b, c, d) who demonstrated actual SMR amplitude control.

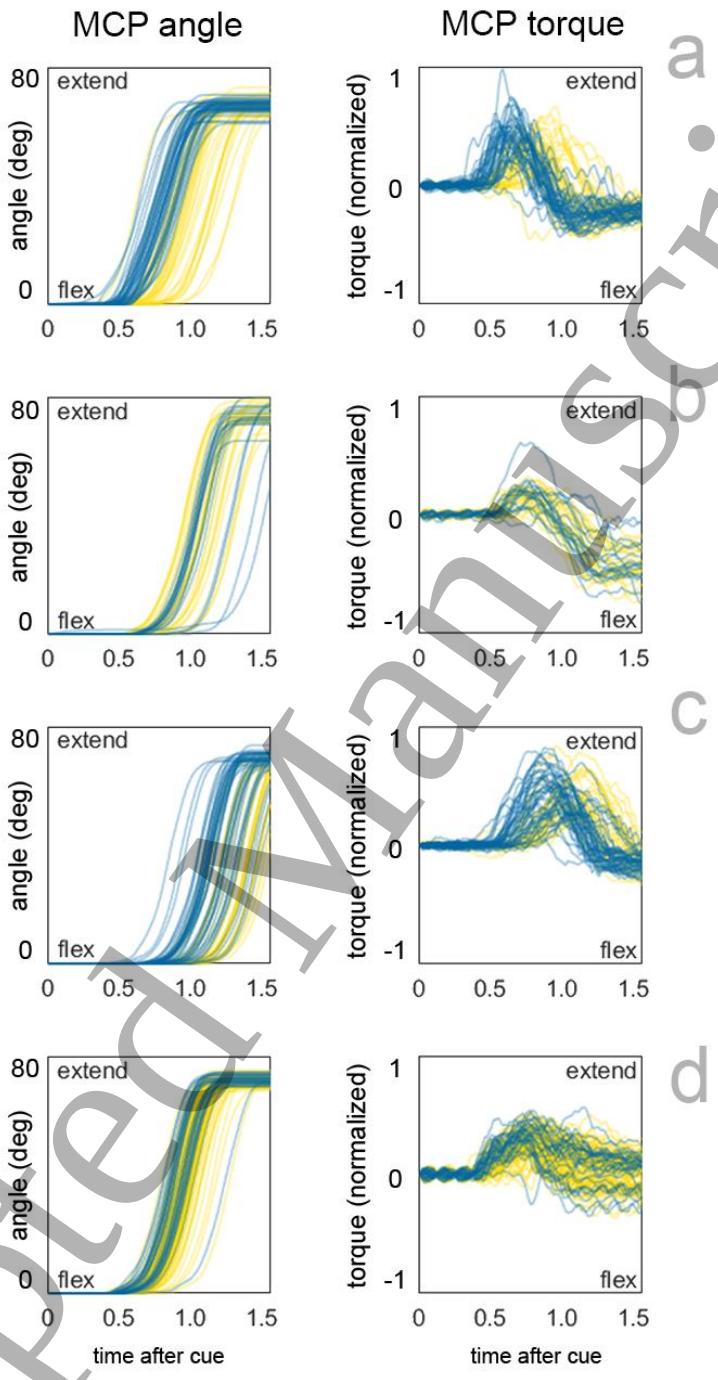

Figure 6: All phase-3 index finger movements from participants a, b, c, and d. Index finger position (left) and normalized MCP torque (right) are plotted vs. time where t=0 corresponds to the movement cue. Yellow traces represent responses to stimuli that increased SMR and blue traces represent responses to stimuli that decreased SMR. Movement latencies were significantly shorter for a, c, and d when they decreased pre-movement SMR amplitude vs. when they increased it. MCP torques were significantly higher for participants a and c when they decreased pre-movement SMR amplitude. Note that the torque values were normalized by the maximum torque generated by each subject in all three different finger movement conditions, although only the index finger movements are shown here.

We performed two-way ANOVAS for each dependent motor performance measure (latency to movement initiation and maximum MCP extension torque) where the finger target (index, middle, both) and SMR condition (increase, decrease) served as independent variables. Analysis across participants showed that SMR condition and the finger used had significant effects on movement latency ($p<0.001$) with no interaction effects ($p=0.443$). SMR condition ($p=0.012$) and finger ($p<0.001$) also had significant effects on maximum MCP torque with no significant interaction effects ($p=0.557$).

We also performed two-way ANOVAs within the four participants (a, b, c, d) with significant narrow-band BCI control at the end of Phase 2. Three of four participants showed significantly reduced latency when they decreased SMR amplitude (two-way ANOVA, participants **a**, **c**, **d**, $p<0.001$; participant b, $p=0.540$). Two of four participants showed significantly higher MCP torques when they reduced SMR amplitude (two-way ANOVA, participant **c**, $p=0.034$; subject **d**, $p=0.007$). Post-hoc analysis revealed higher torques in individuated finger extensions for two participants (t-test, participant **a**, index $p=0.012$, middle $p<0.01$; participant **d**, index $p=0.017$, middle $p<0.01$) and higher torques in coordinated finger extensions in one participant (t-test, participant **c**, both $p=0.04$). One participant showed an interaction effect with finger condition (two-way ANOVA, participant **a**, target-finger interaction, $p=0.001$) where index finger torques were higher with decreased SMR amplitude and middle finger torques were lower with decreased SMR amplitude.

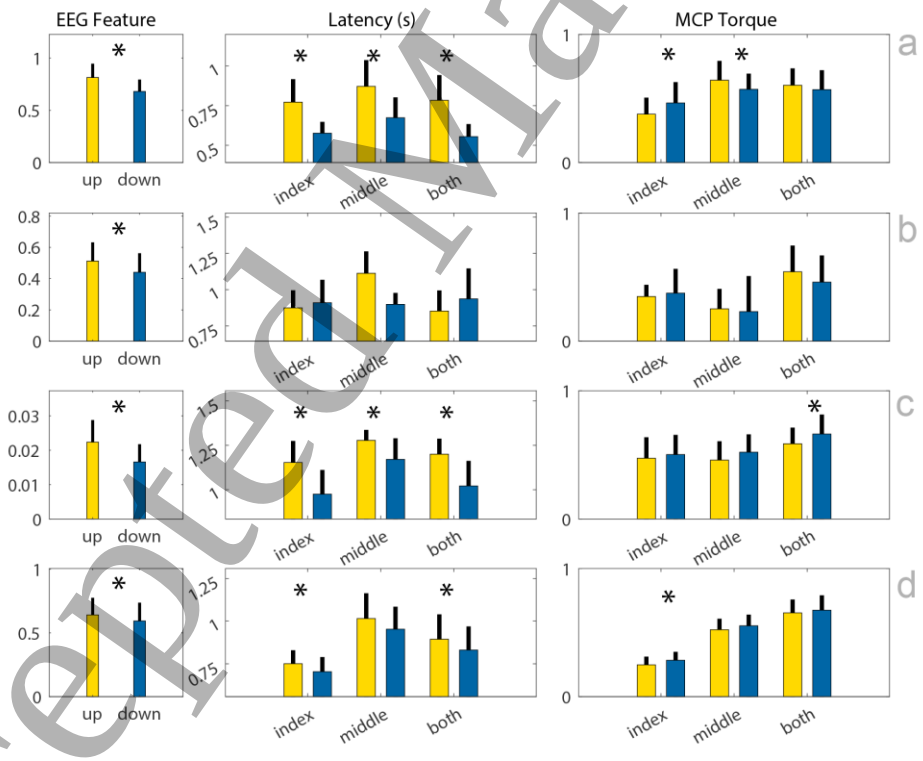

Figure 7: SMR amplitudes and corresponding Phase-3 performance for each movement (i.e. index finger, middle finger, both fingers) from participants a, b, c, and d for SMR increase (yellow) and SMR decrease (blue) trials. Left: Average pre-movement SMR amplitude; Middle: Average l*atencies to movement onset; Right: Average peak MCP torques. Stars indicate significance (p<0.05) and black bars indicate standard error. When SMR amplitude was lower, latencies for Participants a and c were significantly shorter for all*

three movements, and latencies for Participant d were significantly shorter for index and both-finger movements. When SMR amplitude was lower, Participant a had significantly higher torque for index finger movement but significantly lower torque for middle finger movement; Participant c had significantly higher torque for both-finger movement, and participant d had significantly higher torque for index finger movement.

Functional Impact of Training

The clinical outcome measure used in this study to test hand function was the Box & Block Test (BBT) (Radomski and Latham 2008). Mean BBT score at screening was 14.3 +/-10.0 (SD). For comparison, the average score for an unimpaired male age 60-64 is 71.3 +/-8.8 (Mathiowetz, Volland et al. 1985). We observed no significant effects of age, days-post-stroke, type of stroke (hemorrhagic/ischemic), or dominant hand on BBT score. We measured the change in BBT score as the difference in the score at the end of therapy compared to the mean of the values at screening and session 1. The mean change in BBT score after therapy was 4.3 +/-4.5 with minimum and maximum changes of 0 and 12, respectively. BBT scores improved 7.3 +/- 7.5 blocks in the participants with SMR control and 3.5 +/- 3.1 in those who did not gain SMR control or did so with broadband spatiospectral activity indicating artifactual (i.e., head/neck muscle-based) control. The difference between these groups was not significant (two-sample t-test, p=0.199).

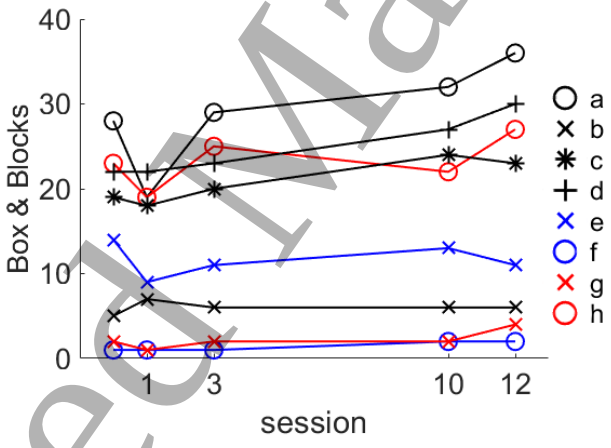

Figure 8: Box & Block scores for each participant taken at baseline and the beginnings and ends of phase 1 (sessions 1 and 3) and phase 3 (sessions 10 and 12). Participants who gained SMR control are shown in black. Participants e and f, who used broadband (i.e., muscle-based) activity to control the BCI, are shown in blue. Participants g and h, who did not gain any control, are shown in red.

Participants with higher baseline hand function had significantly better motor outcomes following the BCI-based training. BBT score at screening predicted the change in BBT score over the course of training for all participants (Spearman Correlation, Fig. 9, left, ρ=0.763, p=0.037). The strength of this effect was improved by limiting the model to the participants with BCI control but was not significant due to the small sample size of N=4 (ρ=1.000, p=0.083). The reduction in movement latency was similarly correlated (latency decreased more for participants with higher BBT score at baseline) for participants with BCI control, but again was not significant (Fig. 9, right, ρ=-1.000, p=0.083). This effect was not present across all participants (ρ=0.000, p=1.000).

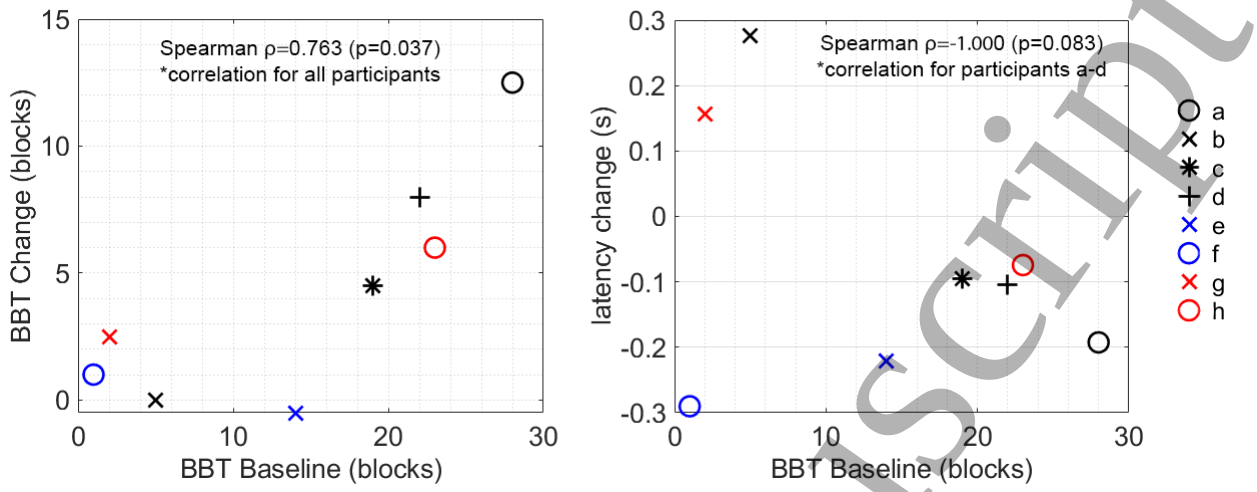

Figure 9: Left: Box & Block Test (BBT) score, measured at baseline, was correlated with a change in BBT score after therapy, measured as the change in score at the end of therapy compared to the average of the baseline and session 1 score. Higher BBT scores at baseline were correlated with larger gains in BBT score after therapy for all participants. Right: Relationship between BBT measured at baseline and the change in latency for finger movements after therapy (session 12 vs. session 1). Positive change in latency values indicates slower response times and negative values indicate faster response times. Higher BBT scores at baseline were correlated with larger reductions in latency after therapy for participants with BCI-control (a-d). Participants e and f, who used artifactual (i.e., head/neck muscle-based) activity to control the BCI, are shown in blue. Participants g and h, who did not gain control of the BCI, are shown in red.

Participants completed a survey at the end of the last day of training. All participants reported that they enjoyed the therapy and that it motivated them to work hard. Participants a, b, c, and d, who all learned to control the BCI, reported specific measures of hand movement/activity that they could do at the end of therapy but not before (e.g., “hold or carry a bag weighing 10 lbs,” “hold a magazine,” “extend [my] fingers and relax [my] hand.” Participant e, who controlled the system using muscle activity rather than brain activity, reported no new activities after training and participant f reported they were “[able to] turn wrists.” Participants g and h, who did not gain control of the BCI, reported some improvement, e.g. “move my fingers a little better”, “relax hand”.

DISCUSSION

In this study, four of eight people achieved statistically significant SMR amplitude control by the end of phase 2, two showed artifactual (i.e., muscle-based) control, and two showed no significant control. In the four people with SMR control, we assessed the effects of such control on movement performance. In three out of these four people, modulating SMR amplitude during movement preparation altered subsequent movement performance. When the participants decreased pre-movement SMR amplitude, movement latency was shorter and movement force was higher. Clinical scores of hand function at baseline correlated with change in hand function after training, although the sample size was small.

Differences in SMR after stroke

Seven of the eight participants in this study exhibited clear ERD patterns prior to movement. However, the topographical representation of this effect was more broadly distributed (Fig. 4) than was found with

a similar protocol for unimpaired individuals (McFarland, Sarnacki et al. 2015). This is a known phenomenon: movement-related signals are often more widely distributed in people with stroke (Cramer, Nelles et al. 1997). They are also known to be significantly smaller in magnitude for people with stroke than in those without impairment (Fu, Daly et al. 2006). Despite these confounding effects, we could predict the intent to move in people with chronic stroke over the course of multiple EEG recording sessions and with similar success rates to previous work in people without neurological injury (McFarland, Sarnacki et al. 2015).

Baseline indicators of performance change

The effect of motor cortical power on subsequent movement latency appears to be dependent on participants' performance before training. McFarland et al. found that people with poorer initial performance experienced a *larger* SMR-dependent change in movement latency (McFarland, Sarnacki et al. 2015). Here, we found that people with poorer baseline scores of clinical function (BBT) exhibited a *smaller* SMR-dependent change in performance, although the sample size was small. One key difference between these findings is that, in this study, people had moderate to severe motor impairments as the result of a stroke. To enable force assistance, the robot required the participants to generate small amounts of extension torque in the cued finger(s) and only the cued finger(s). The most severely impaired participants had more difficulty reliably producing this torque, and often could not limit the torque to a single finger. Thus, the more severely impaired people may not have responded as well in this study because they had less residual motor capability. Conversely, in the McFarland study, unimpaired people with higher function at baseline may have experienced a ceiling effect, again limiting performance change. Although further investigation is necessary, these studies present preliminary evidence that training pre-movement SMR to enhance subsequent motor performance may be most effective for people that avoid such edge cases, i.e. people with mild to moderate impairment or unimpaired people starting with modest performance.

Therapeutic effect of BCI-enhanced robot-assisted training on hand movement after stroke

The 8 participants increased their BBT scores from session 1 to 12 by an average of 4.3 +/-4.5 blocks, a modest increase. Interestingly, the improvement in BBT score trended toward being higher for the four participants who demonstrated SMR control (7.3 +/- 7.5) than in the three who did not (3.5 +/- 3.1), although the difference was not significant ($p=0.199$). This trend merits further investigation, ideally with a larger sample size and a control group (e.g., a group that does not modulate SMR amplitude prior to movement).

What are the potential mechanisms by which controlling pre-movement SMR during movement training might induce a therapeutic benefit? BCI feedback of SMR control may be a form of guided mental practice, where only brain states that produce SMR down-regulation are considered successful. Mental practice has been shown to enhance physical performance even in isolation from physical activity (Cocks, Moulton et al. 2014). However, these benefits have not translated well to rehabilitation programs for people with stroke (Malouin, Jackson et al. 2013), perhaps because people with neurological injury struggle to produce brain states consistent with quality movement (without BCI feedback). However, it is likely that physical practice is equally or more important to motor learning and therapeutic benefit (Bernardi, Schories et al. 2013). Controlling SMR into a movement-favorable state before moving may allow individuals to repeatedly practice movement with improved motor cortex excitability (Pichiorri, De Vico Fallani et al. 2011), thereby improving learning (Stinear, Barber et al. 2008, Stinear, Petoe et al. 2014, Hsieh, Wu et al.

2017). Sensory feedback may also play an important role. Using the same FINGER exoskeleton and participants with chronic stroke with a similar range of initial hand function, we recently found that the functional benefit of three weeks of robot-assisted finger movement practice (again measured by BBT score) depended on the integrity of finger proprioception at baseline (Rowe, Chan et al. 2017). Participants with poor baseline finger proprioception did not benefit from FINGER training. Additionally, we and others found previously that ERD is related to the generation and processing of afferent input (Formaggio, Storti et al. 2013, Norman, Dennison et al. 2016); in our recent study, participants who remained relaxed exhibited ERD when the FINGER robot moved their fingers in a predictable way. Learning to control SMR before attempting finger extension may better prepare sensorimotor systems to receive the afferent information that is important for driving motor learning after stroke.

BCI-based protocols have been suggested as new therapies for people with stroke, with an emphasis on people with more severe motor impairment (Daly and Wolpaw 2008). In contrast, the present results suggest that baseline BBT scores correlate positively with the change in BBT score caused by training (Fig. 9). That is, people with a higher hand function score at screening tended to have a larger increase in hand function after training, although the sample size was small. The present finding may also be contrasted to the results from the Rowe et al. study (Rowe, Chan et al. 2017), in which participants with lower hand function score (but still BBT > 0) showed a greater benefit from FINGER-assisted training. It may be that BCI-assisted robotic training and non-BCI robotic finger training can be matched to different types of individuals, to optimize person-specific results.

Limitations

We selected participants with intact primary somatosensory/motor cortices on the premise that they would be able to generate SMR activity and that their EEG patterns would be more easily interpreted compared to people with damage to these areas that might alter the propagation of electrical activity from the remaining cortical and subcortical regions to the scalp. However, many strokes do damage primary somatosensory and motor cortices, and thus future studies should include persons with such damage. Identifying patient-specific SMR features that correspond to the intent to move, as we did here, may improve the robustness of the SMR training approach when there is damage to specific brain regions. It will be important to analyze the results of BCI-enhanced, robot-assisted training based on lesion location.

Four of the eight participants did not demonstrate significant SMR control, two because of muscle activity contamination and two because they could not reliably generate differences in the selected features. Although most people can learn to control SMR-based BCIs, a non-negligible portion do not. About 20% of unimpaired individuals do not achieve SMR control with prevailing training methods (McFarland, Sarnacki et al. 2005). This failure rate may be higher in people with strokes, even though these individuals do typically exhibit movement-related SMR modulation, albeit with reduced amplitude (Fu, Daly et al. 2006). EMG contamination appeared to preempt acquisition of actual SMR control in two of the participants. This problem can occur in unimpaired individuals as well, and methods for preventing it have been suggested (Goncharova, McFarland et al. 2003). It is of interest that these two participants were observed to have increased tone in the hand and difficulty relaxing the hand during the BCI trials, and, as noted in the results, increased neck tone and shoulder movement during trials. The relationship of EMG contamination to impairment level is an important direction for future study.

This is the initial test of SMR-based training of pre-movement brain state to improve subsequent motor performance in people with stroke. The sample size was small; 4 of 8 people achieved SMR control and 3

of those improved their finger extension ability, as measured by the robot. Increases in clinical outcome, measured by the BBT, were modest but encouraging. This study showed that this methodology is feasible in a fraction of people with stroke; its therapeutic efficacy is not yet clear. Future work must study many more people and include appropriate control groups.

Conclusion

BCI technology, paired with robot-assisted movement practice, has shown promise as a tool for enhancing motor recovery after stroke. In the approach studied here, training participants to down-regulate sensorimotor rhythms before movement immediately enhanced the ensuing movements for some participants. This approach may also enhance motor learning, manifested as changes in functional hand performance. These results merit further investigation in a larger population of people with motor impairment after stroke in a rehabilitation context.

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