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Laterality of brain activity during motor imagery is modulated by the provision of source level neurofeedback

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ABSTRACT

Motor imagery (MI) may be effective as an adjunct to physical practice for motor skill acquisition. For example, MI is emerging as an effective treatment in stroke neurorehabilitation. As in physical practice, the repetitive activation of neural pathways during MI can drive short- and long-term brain changes that underlie functional recovery. However, the lack of feedback about MI performance may be a factor limiting its effectiveness. The provision of feedback about MI-related brain activity may overcome this limitation by providing the opportunity for individuals to monitor their own performance of this endogenous process. We completed a controlled study to isolate neurofeedback as the factor driving changes in MI-related brain activity across repeated sessions. Eighteen healthy participants took part in 3 sessions comprised of both actual and imagined performance of a button press task. During MI, participants in the neurofeedback group received source level feedback based on activity from the left and right sensorimotor cortex obtained using magnetoencephalography. Participants in the control group received no neurofeedback. MI-related brain activity increased in the sensorimotor cortex contralateral to the imagined movement across sessions in the neurofeedback group, but not in controls. Task performance improved across sessions but did not differ between groups. Our results indicate that the provision of neurofeedback during MI allows healthy individuals to modulate regional brain activity. This finding has the potential to improve the effectiveness of MI as a tool in neurorehabilitation.

Introduction

The acquisition of a motor skill is achieved through alterations in brain activity that occurs as a result of practice (Boe et al., 2012; Doyon and Benali, 2005; Halsband and Lange, 2006). While physical practice is the foundation for motor skill acquisition, motor imagery (MI), the mental rehearsal of physical tasks in the absence of overt muscle contraction (Jeannerod and Frak, 1999), has been shown to be an effective adjunct for skill acquisition in numerous disciplines (Arora et al., 2011; Lebon et al., 2010; Schuster et al., 2011). The similarity in spatial activation patterns observed in the brain between real and imagined movement provides the basis for understanding why MI is an effective adjunct to physical practice (Lacourse et al., 2005; Miller et al., 2010; Orr et al., 2008). Specifically, the repetitive activation of neural pathways during MI forms the basis for short- and long-term plasticity that underlies motor learning (Nudo and Milliken, 1996; Nudo et al., 1996). In addition to facilitating skill acquisition in sport and other skilled motor tasks, MI is emerging as a useful adjunct treatment in neurorehabilitation (Barclay-Goddard et al., 2011; Braun et al., 2006). In particular, MI can be coupled with standard therapies in individuals with upper limb (UL) dysfunction post-stroke to better support functional recovery (Nilsen et al., 2010; Page et al., 2011; Riccio et al., 2010). Coupling MI with standard therapies used in stroke rehabilitation can aid recovery in patients with a range of UL impairment (e.g., good, little or no UL function) owing to the low intensity of resources and decreased physical 'cost' required to perform MI (Barclay-Goddard et al., 2011; Braun et al., 2008; Page et al., 2007).

An essential component of skill acquisition is the provision of feedback (Newell, 1991; Newell and Ranganathan, 2009; Winstein, 1991). Feedback permits the assessment of actual versus planned performance, including the identification and correction of errors (Salmoni et al.,

Abbreviations: ECD, equivalent current dipole; EEG, electroencephalography; EMG, electromyography; ERS, event-related synchronization; ERD, event-related desynchronization; fMRI, functional magnetic resonance imaging; HPI, head position indicator; LME, linear mixed-effects; MEG, magnetoencephalography; MI, motor imagery; SEF, somatosensory evoked field.

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1984; Schmidt, 1976). An individual performing MI does not receive feedback however, limiting their knowledge of if, and how well, they are imagining the movement. Thus, the effectiveness of MI may be limited by the lack of feedback. This limitation could be overcome by the provision of feedback to the individual via real-time depiction of the brain activity underlying performance. Further, region-specific neurofeedback could also prove helpful in guiding an individual to modulate the activity of particular brain regions. This feature would be particularly salient in rehabilitative applications, where emerging evidence indicates that the laterality of brain activity parallels the degree of achievable functional recovery (Askim et al., 2009; Chieffo et al., 2013; Dong et al., 2006).

Numerous studies have shown that individuals receiving neurofeedback based on sensor-level analysis of magneto- or electroencephalography (MEG and EEG respectively) data can modulate task-related brain activity over repeated sessions (Bai et al., 2014; Buch et al., 2008; Ono et al., 2013; Soekadar et al., 2011). While effective for some applications, sensor-level analysis lacks the spatial specificity needed for applications requiring neurofeedback from targeted brain regions. This level of spatial specificity however can be achieved using neurofeedback based on source level brain activity. For example, Florin and colleagues recently demonstrated the use of neurofeedback derived from real-time source level analysis of MEG data to successfully modulate activity in selected brain regions (Florin et al., 2013). This work builds on previous source level neurofeedback studies demonstrating modulation of alpha band power fluctuations (Sudre et al., 2011) and increased coherence between two distinct cortical regions (Ora et al., 2013). Similarly, the provision of neurofeedback using real-time functional magnetic resonance imaging (fMRI) has enabled the modulation of brain activity in a region-specific manner including the primary motor cortices (Chiew et al., 2012; deCharms et al., 2004) and anterior cingulate (Caria et al., 2007; deCharms et al., 2005).

It is known that repetition of a task is sufficient to drive changes in brain activity. Neurofeedback studies that do not include a control group who perform MI without neurofeedback cannot disentangle neurofeedback-induced changes in brain activity from the aforementioned practice effect. As such, the inclusion of a no feedback control group is necessary to establish the critical role of neurofeedback in driving changes in brain activity. The lack of a control group in source level MEG or EEG studies creates a knowledge gap related to the role of neurofeedback. Filling this knowledge gap would provide key evidence for the role of MI with neurofeedback in facilitating changes in brain activity.

The present study aimed to identify neurofeedback as the factor driving changes in brain activity during MI. We examined the effect of neurofeedback from the left and right sensorimotor cortex, compared to a no feedback control group, on brain activity underlying MI. A secondary objective was to determine if neurofeedback led to greater improvement in the actual performance of the task being imagined. To achieve these objectives, subjects performed actual and imagined movements over three consecutive days. We hypothesized that, over time, brain activity would lateralize to the sensorimotor cortex contralateral to the imagined movement, with this effect observed for the neurofeedback group only. Further, we hypothesized that the actual task performance would improve in both groups as a function of time, with superior performance observed in the neurofeedback group.

Methods

Subjects

Eighteen right handed (Oldfield, 1971) subjects (8 male, 24.7 ± 3.8 years) agreed to participate in the study. All subjects were free of neurological disorder and each provided written, informed consent. Prior to the onset of the study, subjects were screened for compatibility with MEG (e.g., magnetic artifacts) according to institutional procedure. Subjects were randomly assigned to either the neurofeedback (FB) or control group based on the order of recruitment using a table generated prior to study onset. The study was conducted with approval from the Research Ethics Board at the IWK Health Centre.

Experimental task/paradigm

Regardless of group membership, subjects attended three experimental sessions performed at approximately the same time on consecutive days. A familiarization session immediately preceded the first experimental session during which subjects watched a gender-matched video describing the type of MI to be performed (i.e., kinesthetic, from the first-person perspective) and the task to be performed/imagined. The task used was a sequential button press paradigm performed with the non-dominant (left) hand. Briefly, a seven-digit sequence (4-2-3-1-3-4-2) was performed using a four-key response pad (Photon Control Inc. Burnaby, BC, Canada), with the numbers 1–4 representing the index, middle, ring and little finger respectively. The script accompanying the video emphasized the poly sensory aspects of MI, directing the subjects to attend to sensory information related to task performance (e.g., the feeling of the fingers moving up and down, and the clicking of buttons as they are pressed), which has been shown to facilitate MI performance (Braun et al., 2008). Following the video, participants observed the button sequence, completed the sequence with visual cues, and finally completed the sequence with no visual cues to establish equivalent task proficiency across participants.

All three experimental sessions for all participants included two ten-minute 'test' blocks and two ten-minute 'MI' blocks. Test blocks involved actual performance of the task, and MI blocks involved imagined performance of the task via MI. In all blocks, participants switched between rest and task/MI based on auditory cues provided in 10 s intervals (Fig. 1). Test blocks allowed for the assessment of task performance. During MI blocks, participants in the FB group received neurofeedback based on activity in bilateral sensorimotor cortices.

Neurofeedback enabled the FB group to 'see' the activity in their left and right sensorimotor cortices. Specifically, a bar graph showing side-by-side bars was presented to the FB participants on the projector screen. Following the auditory "Go" cue, real-time activation intensity

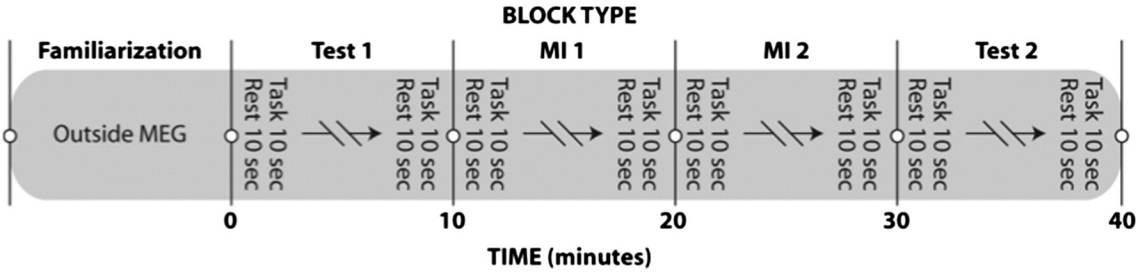

Fig. 1. Protocol timeline. Test and MI components were performed in 10-minute blocks, with participants switching between rest and task/MI based on auditory cues provided in 10 s intervals. A familiarization session occurred in the first study visit only.

(relative to a baseline state) in the two sensorimotor cortices was updated to the bar graph once every second. The bar graph continued to update until one second after the auditory cue to rest, although participants only accessed the feedback at the end of each 10 s MI interval. The bar on the participant's left (labeled with an icon showing a left hand) displayed activation of the right sensorimotor cortex. The bar on the participant's right (labeled with an icon showing a right hand) displayed activation of the left sensorimotor cortex. A fixation cross was used in place of the neurofeedback for the control group.

Neurofeedback was based on event-related synchronization or desynchronization (ERS/ERD) of the beta (15–30 Hz) rhythm in each sensorimotor cortex. A positive neurofeedback signal was displayed when the beta rhythm was reduced with respect to baseline because beta rhythm ERD occurs during MI, movement and somatosensation (Bardouille et al., 2010; Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller et al., 2005; Schnitzler et al., 1997). The seed locations for neurofeedback were located during a 5-minute 'localizer' scan prior to the onset of the first test block. In this localizer scan, percutaneous electrical stimulation of the left and right median nerves elicited the somatosensory evoked response (80 stimuli per side delivered in a randomized order) to localize primary somatosensory cortex. Previous studies have shown that, due to the proximity of primary somatosensory and motor cortices, sources in primary somatosensory cortex are sensitive to activity in both of these areas (i.e., sensorimotor cortex) (Bardouille et al., 2010). Analysis of the evoked response data is described below.

Before the first MI block on each day, a standardized script was read to the participant to reiterate instructions on how to perform MI. All participants were instructed to close their eyes during MI, and open their eyes following the rest cue. Additionally, subjects in the FB group were instructed to utilize the bar graph to assess their performance during MI, which typically occurred at the end of each 10 s MI interval.

Data acquisition

Neuroimaging data was collected using a 306 channel MEG system (Elekta Neuromag Oy, FL). Prior to MEG scanning, electromyography (EMG) electrodes were placed over the corresponding flexor and extensor muscles of the digits (anterior and posterior aspects of the left forearm respectively) using a bipolar configuration with a 1 cm inter-electrode distance. The EMG signals were used to ensure the absence of muscle activity during MI. The electrooculogram was also obtained using four electrodes, with one superior and one inferior to the left eye, and one just lateral to the left and right eye. An electrode attached at the collarbone served as a ground. Additionally, four head position indicator (HPI) coils were placed on the subject's head; two on the forehead and one on each mastoid process. During scanning, HPI coils were activated continuously to generate alternating magnetic fields at frequencies between 293 and 321 Hz. Behavioral (i.e., response pad) data, and event markers indicating the timing of stimuli and responses were also collected throughout. All data were acquired continuously at a sampling rate of 1500 Hz and a bandwidth of 0.1–500 Hz, and recorded to a file for off-line analysis. Simultaneously, one-second data segments were transferred immediately after collection to a 'real-time analysis' computer.

Real-time head position estimation

Real-time head position estimation with one-second temporal resolution was performed during the entire MEG session. During the localizer block, head position estimation provided a quality control measure, wherein the scan was repeated if head translation and rotation exceeded 5 mm and 3 degrees, respectively. During the MI blocks, head position estimation data was used for real-time movement compensation of neurofeedback signals.

Prior to the localizer block, a 5-second scan was performed to establish the initial position of each HPI coil within the helmet. For each coil, temporal signal decomposition was performed at the coil activation frequency to isolate the magnetic field topography generated by the HPI coil. Following this, four recursive least-squares minimizations were performed to determine the magnitude, location and orientation of each coil independently. The values for all four coils defined a rigid body. During all other blocks, magnetic field topographies were also calculated for each coil as described above. A single least-squares minimization was then performed to translate and rotate the pre-defined rigid body from the previous one-second data segment as a single unit. This approach facilitated the real-time application by reducing the processing time for head position estimation by an order of magnitude, as compared to localizing each HPI coil separately.

Head translation (in millimeters) and rotation (in degrees) were displayed at the MEG acquisition station in real-time for quality control. As well, the HPI transformation matrix defining the translation and rotation of the head from the previous data segment was stored for use in movement compensation of source level data (described below). Gradiometer data only were used during head movement estimation and all other MEG data analysis described below, as the magnetometers are more susceptible to environmental noise (Hamalainen et al., 1993).

Real-time source localization (localizer block)

Seed locations for calculating neurofeedback signals were identified in each participant by localizing the somatosensory evoked field (SEF) generated during median nerve stimulation in the localizer block. SEF data were calculated in real-time. Data segments received by the real-time analysis computer were parsed with respect to the onset of stimulation ($-0.1 < t < .3$ s), and separated into epochs based on condition (left/right median nerve). Epochs were low-pass filtered at 70 Hz, baseline corrected with respect to the pre-stimulus interval, and averaged by condition. Following the averaging of 80 trials per condition, the SEF data for each condition were manually inspected for the first prominent magnetic field deflection near 35 ms. For each condition, a single equivalent current dipole (ECD) was fit to this component of the SEF data using a recursive least-squares minimization algorithm.

The ECD localizations for the SEF data were checked manually to ensure that the sources were near the primary somatosensory cortex in each hemisphere. Following this initial verification, the lead-field matrix for each ECD – used to project the 204 channels of gradiometer data down to estimate the source activity – was stored. The lead field matrices were also applied to the SEF data for both conditions to verify that the sources showed independent evoked response patterns of activation, as expected for unilateral median nerve stimulation.

Estimation of MI-related brain activity and provision of neurofeedback

In order to estimate brain activity in left and right sensorimotor cortices during MI blocks, one-second segments of gradiometer data were passed to the real-time computer. Following head position estimation as described above, the positions and orientation of the seed ECDs were updated using the HPI transformation matrix. The lead-fields for each ECD were updated to reflect the new ECD positions and orientation. Following this, the lead field transformations were applied to the MEG data to estimate the time course of source activity during the one-second data segment.

For each estimate of source data, beta rhythm signal power was calculated using a fast Fourier transform. Prior to the receipt of an event marker indicating a "Go" cue, the real-time analysis computer maintained a working memory of the beta rhythm power for the previous four one-second data segments. When an event marker registered the "Go" cue, the beta rhythm power estimates in the previous four one-second data segments were averaged to provide a baseline level of

activation. During MI, the beta rhythm power in the completed portion of the MI interval was calculated, and the change from baseline (i.e., ERS/ERD) was calculated for each source. ERS/ERD was calculated using the base-2 logarithm of the ratio of MI to baseline beta rhythm power. ERS/ERD values were multiplied by −1 for the provision of neurofeedback such that a positive value indicated desynchronization of the beta rhythm in sensorimotor cortex. For example, a neurofeedback value of 1 during the MI interval indicated that the beta rhythm was halved with respect to baseline. Complete analysis of each data segment, including head movement compensation, source estimation and the provision of neurofeedback, was completed within 500 to 600 ms.

For all participants, beta rhythm ERS/ERD during each second of the active interval was recorded to a file. For participants in the FB group, beta rhythm ERS/ERD for the left and right sources was displayed visually as adjacent bars on one bar graph, updating once per second.

Offline analysis — event-related synchronization

Offline analysis of the EMG data obtained during MI was performed to identify and reject data segments that contained muscle activity. Offline analysis of source estimated data at left and right sensorimotor cortices was performed to calculate MI-related beta rhythm ERS/ERD following the removal of data segments containing muscle activity. For each "Go" cue during the MI blocks, EMG and source estimated data were isolated as epochs including 8 s prior to and 12 s following the cue.

The absence of activity in the left flexor and extensor muscles of the digits during MI for each trial was determined by a comparison between the EMG envelope signal amplitudes in the 10 s following the "Go" cue with the 4 s prior to the cue (rest). A Fourier transform determined the amplitude spectra of the EMG envelope for both intervals. Across all subjects, the strongest amplitudes in the EMG envelope amplitude spectrum were observed between 25 and 100 Hz. A paired *t*-test was used to determine if there was a statistically significant difference in the amplitude spectra between MI and baseline in this frequency range in each trial ($p < 0.05$). Trials for which one or both EMG channels showed a difference in muscle activity between MI and rest intervals were excluded from further analysis.

Sensorimotor cortex activation during MI and rest was determined by calculating beta rhythm amplitude at each source. The time interval used for estimating beta rhythm amplitudes were determined by calculating the grand-average change in beta power over time during MI trials. Briefly, a Morlet wavelet transform (size = 1024 samples) was applied to source estimates for each trial to estimate the signal amplitude over time at frequencies between 4 and 70 Hz (16 frequency bins). For each source, results were averaged across all trials, subjects and sessions, and across frequencies in the beta band. The grand-average change in beta power over time was calculated using the base-2 logarithm approach described above (baseline interval was the 4 s prior to the "Go" cue). Results were plotted for each source to determine the time intervals over which the change in beta power was stable.

The MI interval of each trial was defined as the 7 s of data beginning 3 s following the "Go" cue. The rest interval (for normalization of beta rhythm amplitude) was defined as the 7 s of data ending 1 s before the "Go" cue. These intervals were chosen to avoid transient brain responses at MI onset, and anticipatory responses prior to the cue. Following parsing and EMG-based trial rejection, the remaining source estimated data were concatenated based on condition (MI or rest interval). Transient artifacts due to MEG sensor malfunction were manually removed from all source level data. Next, a Fourier transform was applied to the concatenated data, and the signal magnitude was averaged in the beta band. The resultant data represented the strength of the beta rhythm in left and right sensorimotor cortex during MI and at rest for each session and subject.

Actual performance of the motor task in the test blocks was also analyzed offline. For each test trial, the entire sequence of button presses during the 10 s following the "Go" cue was scanned for occurrences of the appropriate button press sequence. The number of correct sequences performed across all trials in a test block was used as the outcome measure to assess changes in performance.

Statistical analysis

We used a linear mixed-effects (LME) regression (Baayen et al., 2008; Bates et al., 2013; Gelman and Hill, 2007; Zuur et al., 2009) to investigate the effects of participant group (FB or control) on the amplitude of the beta rhythm in the left and right sensorimotor cortex during MI and at rest over repeated sessions. The linear mixed-effects model is an extension of the general linear model that is a natural tool for modeling repeated measures (Wu and Zhang, 2006) including multi-session MEG data (Davidson, 2009; Hsu et al., 2011; Weisz et al., 2004). The base model included a four-way interaction between Session, State (MI vs. rest), Hemisphere, and Group, in addition to by-subject random intercepts.

As in previous applications of LME (Newman et al., 2012; Tremblay and Tucker, 2011), we used an iterative model fitting procedure. We first evaluated the addition of by-subject random effects for Session, State, and Hemisphere to the base model. A random effect was retained if there was a significant difference between the log-likelihood ratio of a model that contained the random effect and a model that did not ($p < 0.05$). Only the inclusion of a by-subject random effect for Session was warranted. The significance of interactions and main effects was then evaluated by a comparison of Akaike's Information Criterion (AIC) (Akaike, 1973). More specifically, we removed any fixed effect from the model for which the difference in AIC between a model including it and a simpler one was smaller than 5. However, fixed effects that were part of a higher-order interaction were always kept in the model due to the principle of marginality (Venables, 1998). This procedure has been previously described and validated (Tremblay and Ransijn, 2013; Tremblay and Tucker, 2011).

Statistical analysis of the number of correct sequences followed the same LME modeling procedure described for the source-estimated data. The base model included a three-way interaction between Group (FB vs. control), Session and Block (pre- vs. post-MI), and by-subject random intercepts. The iterative model fitting procedure indicated that a by-subject random effect for Session was warranted ($p = 0.005$). The AIC-based evaluation of interaction and main effects yielded a model with only the main effects of Session and Block. Throughout, values are reported as the mean ± standard error.

Spatial specificity of dipole sources

The spatial specificity of the dipole sources in each sensorimotor cortex was assessed via offline analysis. Briefly, a single dipole was fitted to the left and right SEF data using the peak of the magnetic field (approximately 35 ms). The dipole for the left SEF data was then moved toward the right dipole in 10 mm increments, and the signal strength at the initial location was determined for each increment. This process was repeated for the dipole for the right SEF data, resulting in a sensitivity profile for each source.

Results

Based on offline analyses, 559 trials were discarded due to the presence of muscle activity detected using EMG. This corresponded to 34.5% of the total number of trials performed (1620). Following this, 232 s of data were removed that contained transient artifacts due to MEG sensor malfunction. This corresponded to 3.1% of the total remaining data.

MEG data: seed locations for neurofeedback

Fig. 2 shows the positions of ECDs determined from localization of the left and right SEF data for all subjects and sessions overlaid on a template brain. The dipole locations appropriately overlay the left and right sensorimotor cortices. Grand-average lead fields for the two dipoles determined during the localizer block are also shown in Fig. 2, with planar gradiometers at each sensor location combined using a sum of squares calculation. The sensors that are most sensitive to activation in each sensorimotor cortex are clearly disambiguated on the left and right frontal sensors. Results showing the spatial specificity of the two sources (left and right) are shown in Fig. 3. As the right source is moved toward the left source, the source amplitude for left SEF data decreases as a function of distance from the initial dipole location. The same is true for the left source. In both cases, the source amplitude has reduced by 80% at the midline. This indicates that the left source is insensitive to activation at the right source, and vice versa.

MEG data: beta power

Fig. 4 shows the grand-average change in beta power for MI trials. Beta rhythm ERD begins in the 1 s prior to the "Go" cue, with desynchronization increasing for the first 3 s of the MI interval. Beta rhythm ERD ends 10 s later when the participant hears the "Rest" cue, and is followed immediately by 2 s of beta rhythm ERS (i.e., post-MI "rebound"). Based on the beta rhythm time course, MI-related beta rhythm strength was determined in the 7 s beginning 3 s following the "Go" cue. Rest-related beta rhythm strength was determined in the 7 s of data ending 1 s before the cue.

Fig. 5 shows the group-averaged percent signal change from baseline for the beta rhythm in each condition, session, and group. The

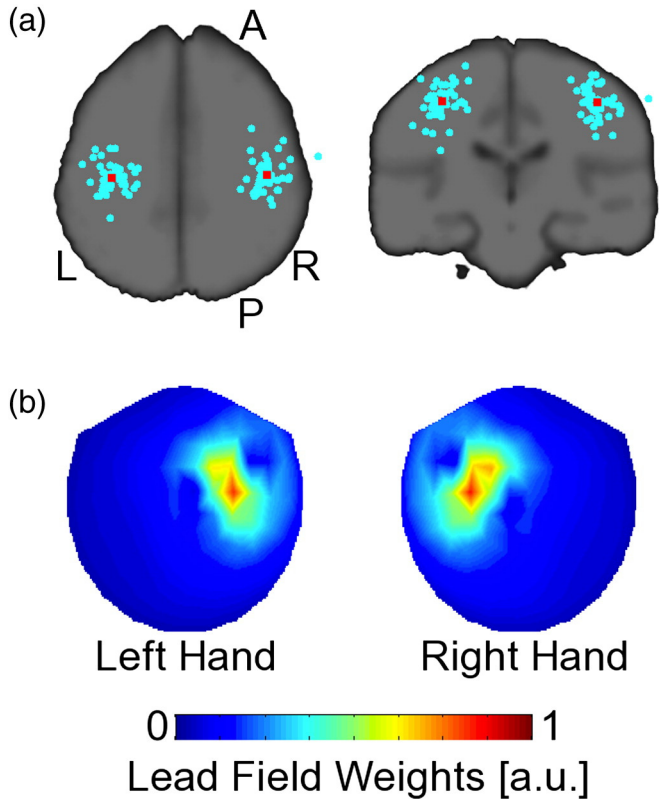

Fig. 2. (a) Seed locations for neurofeedback for all subjects and all sessions are shown as cyan circles. The mean location for each hemisphere is shown as a red square. (b) MEG sensor weights for generating neurofeedback signals for each sensorimotor cortex are shown.

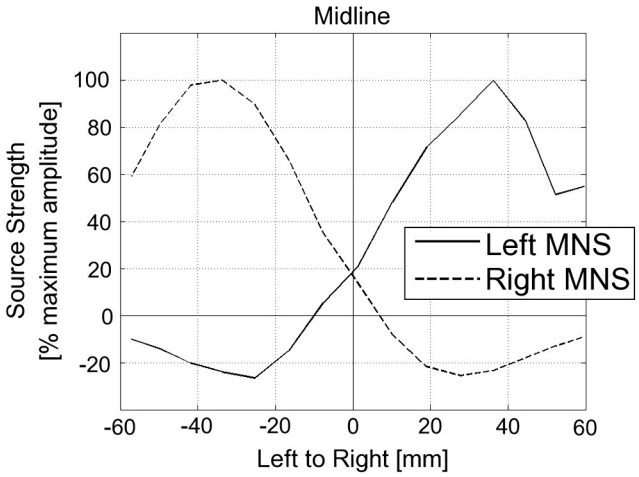

Fig. 3. The spatial specificity of neurofeedback sources is shown for a representative subject. As the dipole location is shifted away from the correct location (i.e., left and right sensorimotor cortex), the somatosensory evoked field (SEF) source amplitude decreases, reaching 20% by the midline. This finding indicates that each dipole is sensitive to activity in contralateral sensorimotor cortex only.

FB group shows decreasing right (i.e., contralateral to imagined movement) sensorimotor cortex beta rhythm amplitudes over repeated sessions occurring during MI and rest. Decreased beta rhythm amplitude indicates that the FB group increases the activation of contralateral sensorimotor cortex over repeated sessions. Increased activation of contralateral sensorimotor cortex occurred during MI and the rest interval. A similar pattern is not observed in the left (i.e., ipsilateral) sensorimotor cortex, which shows little change in beta rhythm amplitude during MI or rest. The control group exhibits decreasing ipsilateral sensorimotor cortex beta rhythm amplitudes over repeated sessions during MI. This decrease in beta rhythm amplitude indicates that the control group increases MI-related activation of ipsilateral sensorimotor cortex over repeated sessions.

The most likely LME model for beta rhythm amplitude included a significant three-way interaction *Session* × *Group* × *Hemisphere*, a significant two-way interaction *Group* × *Hemisphere*, and a significant main effect of *State*. Given the three-way interaction, we do not interpret the two-way interaction, according to the principle of marginality (Venables, 1998). The main effect of State indicated that beta rhythm

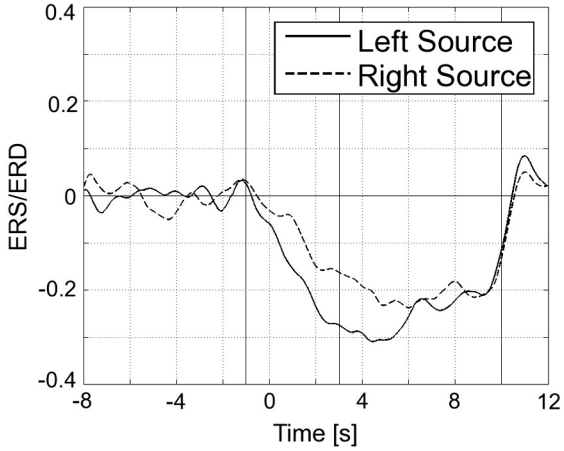

Fig. 4. The grand-average change in beta power for MI across all trials, blocks, sessions, subjects, and groups is shown. Data are shown for sources in both left and right sensorimotor cortices. Both sources exhibit increasing beta rhythm event-related desynchronization beginning just prior to the "Go" cue ($t = 0$ s) that becomes a sustained response ~3 s following the "Go" cue. A small beta rhythm event-related synchronization occurs immediately following the "Rest" cue.

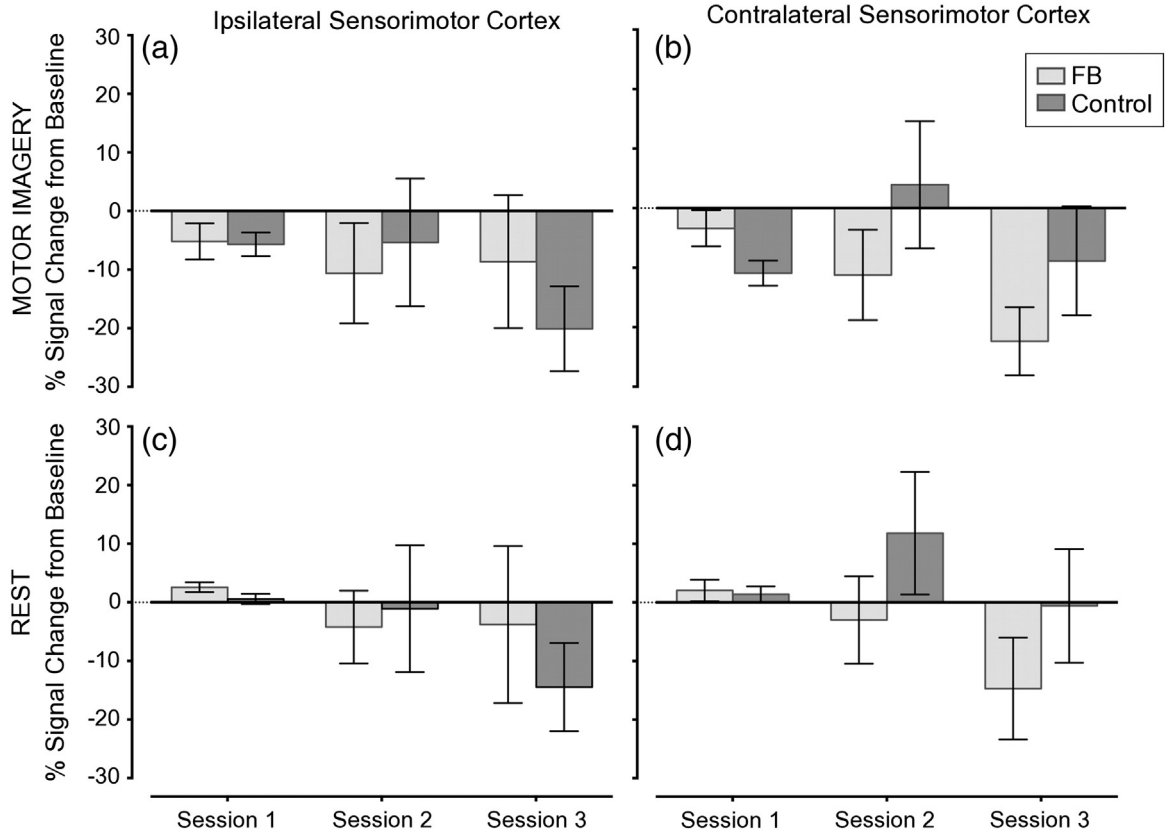

Fig. 5. Percent signal change from baseline for the left and right sensorimotor cortex in the FB (light gray) and control (dark gray) groups across sessions for MI (a, b) and rest (c, d). Bars represent standard error. As predicted, across sessions, participants in the FB group show stronger beta rhythm desynchronization of the sensorimotor cortex contralateral to the imagined movement during imagery and at rest. Participants in the control group show stronger beta rhythm desynchronization of the sensorimotor cortex ipsilateral to the imagined movement across sessions.

amplitudes were lower during MI than at rest (Active = −6.08%; Resting = 0.99%; Difference = −7.07%, Std. Error = 1.48%, $t(131) = -4.79$, $p < 0.001$). This corresponds to the pattern of MI-related beta rhythm desynchronization in sensorimotor cortices expected in this study, and described previously (Pfurtscheller et al., 2005; Schnitzler et al., 1997). We deconstructed the three-way interaction (*Session* × *Group* × *Hemisphere*) by performing a post-hoc analysis with three contrasts in the third session. We investigated whether there was a significant difference ($p < 0.05$) between (1) contralateral minus ipsilateral beta rhythm amplitudes in the FB and control groups, (2) contralateral and ipsilateral beta rhythms in the FB group, and (3) contralateral and ipsilateral beta rhythms in the control group. Probability values were two-tailed and Bonferroni corrected for three comparisons.

Results of the post-hoc analysis indicated that the difference between the contralateral and ipsilateral beta rhythm amplitudes in Session 3 was significantly more positive in the FB than the control group (difference = 24.87%, Std. Error = 5.12%, $t(131) = 4.86$, $p < 0.001$). This result established that the FB and control groups had inter-hemispheric differences in beta rhythm amplitude in Session 3. For the FB group, the beta rhythm amplitude in the contralateral hemisphere was significantly more negative than in the ipsilateral hemisphere in Session 3 (contralateral = −14.99%, ipsilateral = −2.68%, difference = −12.31%, Std. Error = 3.62%, $t(131) = -3.4$, $p = 0.003$), but the reverse was true in the control group (contralateral = −1.18%, ipsilateral = −13.74%, difference = 12.55%, Std. Error = 3.62%, $t(131) = 3.47$, $p = 0.002$). These two results taken together establish that, by Session 3, the FB group had stronger contralateral than ipsilateral beta rhythm ERD, and the control group demonstrated the reverse pattern. Results are summarized in Table 1 and the three-way interaction is illustrated in Fig. 6.

Behavioral data: number of correct sequences

There was a main effect of Session on task performance — defined as the number of correctly executed sequences in a test block. This main effect indicated that participants got better at the task (40 ± 3, 52 ± 4 and 57 ± 4 for Sessions 1, 2 and 3 respectively), but this improvement did not differ between the FB and control groups. Post-hoc analysis revealed that the number of correctly executed sequences differed significantly between Sessions 1 and 2 (difference = 12, Std. Error = 2, $t(32) = 6.74$, $p < 0.001$), between Sessions 1 and 3 (difference = 16, Std. Error = 2, $t(32) = 8.63$, $p < 0.001$), and Sessions 2 and 3 (difference = 16, Std. Error = 1, $t(32) = 3.48$, $p = 0.002$). Post-hoc test values were Bonferroni corrected for three comparisons. There was also a main effect of Block on task performance. This effect indicated

Table 1
Results summary for beta power changes.

	Df[a]	Sum Sq[b]	Mean sum Sq[c]	F	*p* value	Dev Expl[d]
Group	1	0.012	0.012	1.0	0.314	0.10
Session	2	0.030	0.015	1.3	0.288	0.26
State	1	0.270	0.270	22.9	<0.001	2.34
Hem[e]	1	0.015	0.015	1.3	0.258	0.13
Group × Session	2	0.014	0.007	0.6	0.556	0.12
Group × Hem	1	0.161	0.161	13.7	<0.001	1.40
Session × Hem	2	0.045	0.022	1.9	0.155	0.39
Group × Session × Hem	2	0.173	0.086	7.3	0.001	1.50

[a] Numerator degrees of freedom (denominator degrees of freedom = 131).
[b] Sum of squares.
[c] Mean sum of squares.
[d] Percentage of the deviance explained.
[e] Hemisphere.

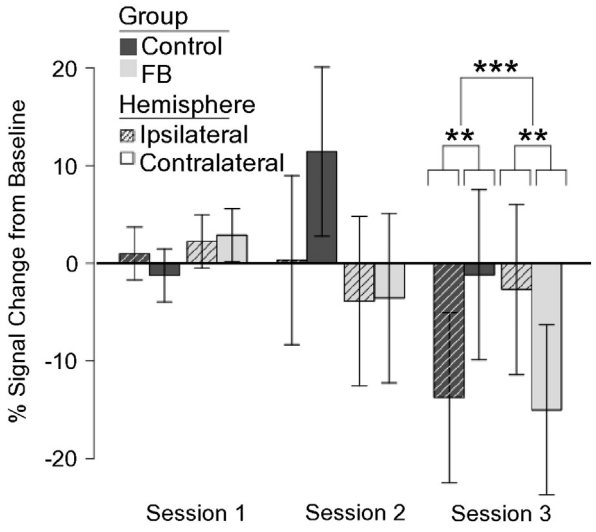

Fig. 6. Three-way interaction for percent change in beta power from rest by session for the FB (light gray) and control (dark gray) groups. Bars with diagonal shading lines are for the ipsilateral hemisphere, whereas bars without shading lines are for the contralateral hemisphere. Bars represent +/- 1 standard error of the mean. The dendrogram above the bars in session 3 represent the results of the post-hoc analyses. ** indicates significance at $p < 0.01$; *** indicates significance at $p < 0.001$. As outlined in the Results section, all comparisons were Bonferroni corrected for three comparisons.

that participants improved at the task from the start of each session (pre-MI) to the post-MI test (pre = 40, post = 47, difference = 7, Std. Error = 1, $t(32) = 6.6$, $p < 0.001$). Again, this improvement did not differ between groups. A summary of these results is provided in Table 2.

Discussion

This study used a two-group design to identify neurofeedback as the primary factor driving changes in MI-related brain activity over repeated sessions. Specifically, we showed that neurofeedback from bilateral sensorimotor cortices leads to a more contralateral pattern of MI-related brain activity over sessions, as compared to a no feedback control group. Thus, we establish that providing feedback about the brain activity underlying MI of a unilateral motor task improves an individual's ability to modulate activity in specific regions of the brain. The provision of neurofeedback did not lead to more effective motor skill acquisition, as compared to the control group. That is, over the course of three consecutive days, the neurofeedback-induced change in brain activity did not correspond to better task performance. Further interpretation of this result is provided below.

We have established that neurofeedback provides an effective means to guide the modulation of regional brain activity during MI. Specifically, we observed increasing levels of ERD, indicative of increased brain activity, in the contralateral sensorimotor cortex during MI in the FB group only. The lateralized brain activity observed in the FB group leads to the conclusion that neurofeedback aids MI performance to the extent that the individual is able to govern the underlying pattern of brain activity. This finding builds on prior case studies indicating that MEG-based source level neurofeedback enables an individual to modulate regional brain activity (Florin et al., 2013; Ora et al., 2013; Sudre et al., 2011). This finding represents an important addition to MI as an intervention in neurorehabilitation. Akin to other interventions, a goal underlying the recovery of function via MI is to 'normalize' brain activation patterns. Specifically, a shift of brain activity from the ipsilateral to the contralateral hemisphere is related to more complete functional recovery post-stroke (Askim et al., 2009; Dong et al., 2006). Providing region-specific neurofeedback from the left and right sensorimotor cortex during MI may be a means to realize these desired changes in brain laterality in patients post-stroke.

Importantly, utilizing source level analysis provides an opportunity to provide a direct representation of activity occurring at specific regions of interest, which may not be limited to primary sensorimotor cortices. Modifications to the paradigm utilized in the current study would permit the region targeted for neurofeedback to be altered. Specifically, localization of target brain regions could be based on anatomical MRI, or coordinates derived from a template brain. The former approach has been applied in previous MEG-based source level studies, with neurofeedback generated from signals in the frontal (Florin et al., 2013), parietal (Florin et al., 2013; Ora et al., 2013; Sudre et al., 2011) and occipital lobes (Ora et al., 2013; Sudre et al., 2011). Using the real-time analysis technique described in the current study may facilitate the use of region-specific neurofeedback for cognitive impairments such as those affecting attention, as well as for brain computer interface (BCI) applications.

At this point however, it is unclear how many sessions are required to optimize the lateralization of brain activity during neurofeedback-guided MI. The significant effect for brain activity in the FB group was observed as a function of session (Figs. 5 and 6), indicating a training effect whereby participants required repeated exposure to the neurofeedback in order for it to be effective. It is unclear why repeated exposures to neurofeedback were necessary before a change was measured. Acknowledging methodological differences, Florin and colleagues noted significant changes in brain activity after the final training session (Session 8 of 8), with minimal change noted at mid-training (Session 5 of 8) (Florin et al., 2013). Similarly, Buch et al., employing real-time neurofeedback based on sensor level μ rhythm amplitude, noted a significant difference in BCI control by patients post-stroke only after the last of twenty training sessions (Buch et al., 2008). Other studies using sensor level neurofeedback to improve BCI control in patients show similar findings, with moderate success observed after numerous training sessions (Prasad et al., 2010). Clearly, some time is required for a participant to learn to interpret neurofeedback signals and subsequently incorporate these signals into their MI performance. Further research is required to quantify the learning curve associated with neurofeedback-guided MI.

Interestingly, a decrease in contralateral beta rhythm amplitude across sessions was observed not only during MI, but also at rest in the FB group (Fig. 5, panels c and d). The observation of changes in the beta rhythm amplitude in contralateral sensorimotor cortex during resting intervals in the MI blocks may be indicative of a training effect whereby excitability of the cortex is altered. Specifically, a stronger, sustained disinhibition of the functional connections underlying MI performance may be present in later sessions. This notion is supported by recent work demonstrating a facilitation of motor excitability in participants using MI-based neurofeedback and BCIs (Bai et al., 2014; Mokienko et al., 2013). Corroboration of these speculative changes in functional connectivity requires further investigation, including expanding our understanding of the duration of this effect, as it is limited to the time course utilized in the current study.

The increase in beta ERD for the ipsilateral sensorimotor cortex during MI noted for the control group is likely indicative of an inability to selectively perform MI with the non-dominant hand. Numerous studies indicate that MI is a difficult skill to acquire (Bovend'eerdt et al., 2012; Braun et al., 2008; Malouin et al., 2009); ours and previous findings

Table 2
Results summary for behavioral data.

	Df[a]	Sum Sq[b]	Mean sum Sq[c]	F	*p* value	Dev Expl[d]
Session	2	2012.967	1006.483	37.5	<0.001	6.01
Block	1	1166.898	1166.898	43.5	<0.001	3.48

[a] Numerator degrees of freedom (denominator degrees of freedom = 32).
[b] Sum of squares.
[c] Mean sum of squares.
[d] Percentage of the deviance explained.

further support the notion that neurofeedback-guided MI aids the participant in performing MI, presumably because the participant can utilize the feedback to correct errors and optimize their performance.

Motor imagery has been shown to facilitate skill acquisition in numerous disciplines (Arora et al., 2011; Schuster et al., 2011). Accordingly, our results show that engaging in serial sessions of MI-based practice improves motor performance of the task being imagined (Table 2). While actual execution of the task in the test blocks likely contributed to the observed change in performance, previous work indicates that task practice vis a vis the MI blocks would also underlie the improvement. Moreover, our results support the notion that practice via MI leads to changes in performance; we observed a significant improvement in performance between test block 1 and 2 in each session, which bookend the two MI training blocks.

The provision of neurofeedback during MI did not however result in a measureable difference in task performance between groups. Interestingly, much of the literature examining MI coupled with neurofeedback has not focused on behavioral outcomes per se (i.e., improved motor performance of the task being imagined). Rather, studies have focused on outcomes related to changes in brain activity such as the ability to successfully control a BCI. With respect to the current results, we speculate that the task utilized was too simple; while brain activity underlying MI of the task was altered, participants in both groups received sufficient practice to display gains in motor performance. Similar results have been reported previously, whereby one week of physically practicing a hand motor sequence resulted in altered brain activity in the absence of a pre–post training difference in execution errors (Lacourse et al., 2005). Given the overlap between brain areas activated during motor execution and MI (Decety, 1996; Hanakawa et al., 2008; Lacourse et al., 2005; Orr et al., 2008; Porro et al., 1996), it is possible that a similar effect would occur with repeated sessions of MI.

An important methodological issue addressed in the current study is the rigorous rejection of data where MI was performed in the presence of muscle activity. Muscle activity that is concurrent with MI contaminates neuroimaging results by representing a combination of MI- and motor-related brain activity. As such, we eliminated any MI trials in which muscle activity occurred in the relevant flexor and/or extensor musculature in the forearm. Although controlling for muscle activation using EMG is considered the gold standard in MI studies, a scoping review found that only two of seventy-five studies used this approach (Hetu et al., 2013). Several other studies have attempted to control for motor-related activity via visual monitoring; however, this method is sensitive to sizeable overt movements only, and not to small movements that may occur during the performance of MI (Hetu et al., 2013). Given the similarity between MI- and motor-related patterns of brain activity, the importance of trial rejection based on muscle activity in this and future MI studies cannot be overstated.

We chose to provide no neurofeedback signal to individuals assigned to our control group. This approach matches the way in which MI is currently implemented in stroke rehabilitation (Braun et al., 2008; Ietswaart et al., 2006). While the use of a no feedback control group is an improvement over prior study designs, another option would be to provide sham neurofeedback to the control group, or to include sham neurofeedback as a third group. Sham neurofeedback would distinguish the effectiveness of the meaningful neurofeedback from the presence of neurofeedback in general.

We provided visual neurofeedback in this study to ensure that the feedback signal did not interfere with the participant's immediate experience of MI. Closing ones eyes while performing MI is an appropriate strategy for effective imagery (Schuster et al., 2011). As such, participants only have the opportunity to make use of visual neurofeedback at the end of each MI interval. The use of an alternate or dual modality signal (e.g., visual plus auditory or tactile) may be a means to provide neurofeedback in simultaneity with MI. Further research is necessary to establish which modality of neurofeedback is the most effective for lateralizing activity in sensorimotor cortices during MI.

Conclusion

We identify the provision of neurofeedback as the factor driving increased contralateral brain activity during MI of a unilateral motor task. This finding establishes the importance of neurofeedback in improving MI performance. These results provide a foundation for pursuing numerous applications for neurofeedback-guided MI. Specifically, neurofeedback may provide critical information about MI performance to afford an opportunity for patients to modulate regional brain activation. Future work will be pursued in this direction to establish the clinical applicability of neurofeedback.

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