Cortical and behavioral adaptations in response to short-term inphase versus antiphase bimanual movement training

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Abstract Bimanual movement training (BMT) may be an effective rehabilitative protocol for movement-related deficits following a stroke; however, it is unclear how varying types of BMT induce cortical adaptations in the healthy population. Moreover, we lack a methodology to measure cortical adaptations in response to modes of movement training. Therefore, the present study measured the cued movement-related potential (MRP) to investigate cortical adaptations during cued inphase versus antiphase BMT that transferred to a unimanual task and how cortical modulations related to behavior. Three specific hypotheses were investigated: (1) cued inphase BMT would induce cortical adaptations within regions subserving motor preparation and movement execution, (2) repetitive cued unimanual training would induce cortical activity modulations associated with motor execution, and (3) increased cortical activity would be associated with enhanced performance. On three separate days, EEG was recorded from 22 electrodes during three types of cued movement training: inphase BMT, antiphase BMT and repetitive unimanual movement, in addition to pre- and post-training unimanual movement trials involving cued right wrist flexion. The MRP was measured for each repetition during each trial. Results showed a significant training-related increase in preparatory activation correlated with a behavioral enhancement following cued inphase BMT. This effect was not attributable to a change in arousal. No significant training-related modulation occurred in response to cued antiphase BMT or repetitive unimanual movement training. These results suggest that cortical adaptations in relation to the preparation of a cued movement enhance in response to cued inphase BMT, and the MRP is an effective measurement tool to assess training-related adaptations in response to inphase BMT specifically.

Keywords EEG · ERP · Stroke · Neurophysiology · Movement-related potentials

Introduction

Of a variety of treatment strategies, bimanual movement training (BMT) of the upper limbs specifically shows some potential to lead to behavioral and functional improvement in both the subacute and chronic phases of stroke recovery (Cauraugh and Kim 2002; Cuadrado and Arias 2001; Luft et al. 2004; McCombe Waller and Whitall 2008; Mudie and Matyas 2000; Stewart et al. 2006; Whitall et al. 2000). Although evidence suggests that bimanual movement, involving both the damaged and intact hemispheres, may enhance motor-related brain activity in the stroke-hemisphere in some patients (Silvestrini et al. 1998; Staines et al. 2002), the neurophysiological mechanisms that contribute to the benefits of BMT are not yet clear. More specifically, a few studies to date (Luft et al. 2004; Stinear et al. 2008) report cortical activation modulations that underlie observed behavioral improvements following BMT in stroke patients.

In the present study, we chose to take one step back from the stroke patient population and focus upon the healthy
population to explore the possibility of using the cue-related movement-related potential (MRP) to measure cortical activation modulation during a cued BMT session and during a similar unimanual task, to assess potential transfer effects to a one-handed movement. Potential modulatory effects of the cued MRP during and following BMT could elucidate the neurophysiological mechanisms underlying this type of movement training. We were most interested in cortical activation modulations in response to visually cued inphase versus antiphase BMT, and how these two modes of training differentially modulate the cued MRP. Focusing upon the healthy population allowed us to observe the effects of BMT upon the MRP, and associative cortical activation, without the added complication of cortical injury, and it provided control data for potential use in future stroke related studies.

The use of event-related potentials, to measure visuomotor learning in the healthy population, has been demonstrated previously. Staines et al. (2002) reported that the MRP, in response to a visual cue, in addition to an ERP extracted around the presentation of a cue, modulate in response to learning a novel unimanual visuomotor task using wrist extension. More specifically, the early and late components of the MRP increase in negativity, denoting an associated increase in cortical activation. In another study by Hill (2009), the prominent positive component of a similar ERP enhances in response to visuomotor learning. Therefore, these studies (Staines et al. 2002; Hill 2009) demonstrate that the MRP or other similar types of ERPs can measure cortical modulations during short duration novel visuomotor learning in healthy participants.

A previous study from our laboratory (Smith and Staines 2006) demonstrated that the cue-related MRP can be used to measure training-related cortical adaptations during a cued unimanual task in response to short duration cued BMT that incorporates both inphase and antiphase bimanual movement patterns. Inphase bimanual movement specifically refers to the movements of the homologous effectors in both limbs, such as bilateral wrist flexion or extension. Antiphase movement refers to the movements using the opposite effectors, such as right wrist flexion in conjunction with left wrist extension and vice versa. Our previous study reported (Smith and Staines 2006) that early MRP amplitudes were significantly enhanced during the later portion of the training session and also during performance of a similar unimanual movement following the single practice session. Therefore, preparatory cortical activation was enhanced during the BMT and it transferred to a unimanual task. Although a behavioral assessment was not our primary interest, the enhancement of early MRP amplitude, during the unimanual task, was associated with a decrease in reaction time (RT).

Unfortunately, our previous study (Smith and Staines 2006) could not discern a differential degree of cortical activation adaptation following cued inphase versus cued antiphase BMT. Several transcranial magnetic stimulation (TMS) studies using healthy participants (Stinear and Byblow 2002, 2004) report that inphase bimanual movement disinhibits homologous muscle representations within the primary motor cortex (M1) whereas antiphase movement increases inhibition within the same M1 areas. Therefore, it may have been possible that the inphase component of our bimanual paradigm (Smith and Staines 2006) disinhibits cortical regions, leading to an increase in early MRP amplitude with an associated decrease in RT. In addition, the localization of the early MRP during the cued task is not entirely clear. Potential cortical regions that contribute to the generation of the early MRP include the supplementary motor area (SMA) or the dorsal portion of the lateral premotor cortex (PMd). It is possible that preparatory activity of the cued MRP reflects more PMd activity as opposed to SMA activity. Cued inphase bimanual movement is associated with preparatory activity within the PMd region, whereas antiphase bimanual movement is associated with preparatory activity within the SMA (Seitz et al. 2004; Jancke et al. 2000; Koch et al. 2006; Sugiura et al. 2001).

Primary motor cortical activation and representational extent increase with unimanual movement training (Nudo et al. 1996; Kleim et al. 1998; Plautz et al. 2000; Karni et al. 1995, 1998). The exact temporal and neurophysiological processes underlying cortical modulations in response to unimanual training remain unknown; however, evidence indicates that representational modulations are mediated by a decrease in GABAergic activity, leading to the unmasking of latent horizontal connections within associated M1 representations (Jacobs and Donoghue 1991; Kaas et al. 1983). Our previous study (Smith and Staines 2006) did not demonstrate a modulation of the late MRP likely reflective of M1 excitability following BMT. BMT only led to an enhanced preparatory activation reflected by the early MRP.

Of the few studies that report bimanual transfer effects upon a unimanual movement (Burgess et al. 2007; Schulze et al. 2002; Vangheluwe et al. 2004; Zanone and Kelso 1992, 1997), analysis only pertains to behavioral responses during motor execution opposed to preparation. For example, how well a subject can perform a unimanual movement following a bimanual pegboard task (Schulze et al. 2002) or an asymmetrical bimanual drawing task (Vangheluwe et al. 2004). Overall, studies demonstrate a positive behavioral transfer effect of BMT to a unimanual task; however, studies have yet to investigate the associative underlying cortical activation modulations.

Therefore, in accordance with current literature and our previous findings, we tested the following three hypotheses:
(1) Cued bimanual movement training that emphasized inphase wrist movements would induce larger cortical adaptations within regions subserving motor preparation and execution, as evidenced by changes in the early and late MRPs, respectively, opposed to training that required cued antiphase bimanual wrist movements; (2) Repetitive unimanual training would induce cortical activity modulations only associated with motor execution; and (3) Training-induced cortical adaptations (MRP enhancements) would be associated with enhanced performance (decrease in RT), therefore replicating our previous findings. To investigate the above hypotheses, the present study utilized the MRP determined from a unimanual visually cued task in which participants used flexion of the right wrist to move a cursor to a specified target on a computer screen prior to and following a single session of either bimanual (inphase or antiphase) or unimanual training interventions.

Materials and methods

Subjects

Ten healthy, normal participants (2 men, 8 women; age range 22–35) participated in the study, each providing written informed consent. All were right-handed by self-report and did not report any history of neurological impairments. Participants were paid a nominal fee for their participation. The experimental procedures were approved by the Office of Research Ethics at the University of Waterloo and the research ethics board at the Toronto Rehabilitation Institute.

EMG and EEG recording procedure

Electromyography (EMG) was recorded from the right flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles using bipolar electrodes placed longitudinally over the muscle bellies. Scalp electroencephalographs (EEG) were recorded from 22 electrodes using the international 10–20 system guidelines and an electrode cap (Quick-Cap, Neuroscan, Compumedics, NC). All electrode sites were not employed in quantitative analysis. All EEG channels were referenced to linked electrodes placed on the left and right mastoid processes. Vertical and horizontal eye movements were monitored with bipolar recordings above and below the left eye and at the lateral aspect of the left and right eyes respectively. All channels were amplified (20,000×), low-pass filtered (50 Hz), digitized at a rate of 250 Hz (Neuroscan, Compumedics, NC) and impedance was below 5 kΩ. All post-processing of the EEG data was performed using Neuroscan® (Compumedics, NC).

Behavioral task

All subjects came into the laboratory on three separate days to perform three blocks of visually cued movement trials as follows: pre-training cued unimanual movement (right wrist flexion—40 repetitions), cued inphase/antiphase bimanual movement training (combinations of right/left wrist flexion/extension—160 repetitions) or repetitive unimanual movement training as a control (right wrist flexion—160 repetitions), and post-training cued unimanual movement (right wrist flexion—40 repetitions). Therefore, the experiment was a repeated measures design (all 10 subjects performed each of the training interventions on three separate days). The order of training intervention day (inphase, antiphase and repetitive unimanual training) was randomized across subjects.

For the pre- and post-training trials, it was important to include enough repetitions in order to increase the signal to noise ratio to observe the cued MRP. Forty repetitions were determined to be a sufficient number. For the training trials (trial 2), 160 repetitions were selected in order to observe the cued MRP in the first and last 40 repetitions and to lengthen the training trial to at least 30 min. A previous study by Classen et al. (1998) reported training-related cortical activation modulations following 30 min of movement training.

Subjects were seated in a dimly lit room, in front of a computer monitor with arms and head supported. The medial aspects of bilateral forearms were supported with elbows flexed to 90° and the shoulder in forward flexion ~0–10°. The wrist was oriented in a neutral position so that flexion and extension of the wrist occurred in the horizontal plane. This position was maintained for all trials. Electromyographic sensors (Biometrics, Wales) were placed on the posterior surface of the 3rd metacarpal and the distal forearm of each upper limb in order to measure wrist flexion and extension. The sensors, in conjunction with a customized program written in LabVIEW (National Instruments, Austin, TX), allowed the subjects to control a cursor on a computer monitor by flexing and extending the wrists (Fig. 1). Right wrist extension controlled upward movement of the cursor, and right wrist flexion controlled downward movement of the cursor. Left wrist extension controlled leftward movement of the cursor and left wrist flexion controlled rightward movement of the cursor. Simultaneous right/left wrist flexion/extension produced diagonal movement of the cursor on the screen (Fig. 1b).

Pre- and post-training trials were identical and required subjects to move the cursor (8 mm in diameter) from a starting position to a target (1.5 cm²) displayed in the bottom-center of the screen (Fig. 1a). In order to assess the influence of the three types of training (inphase, antiphase and repetitive unimanual movement) upon the cue-related...
movement-related potential (MRP), it was important for the pre- and post-training trial movement to be discrete and simple. Movement of the cursor was calibrated for each subject so that maximal flexion or extension of the wrist would not allow cursor movement to exceed the target location. Calibration prevented the subject from overshooting the target, which would interfere with accuracy of the task and held movement amplitude (ROM) constant. For the pre- and post-training trials, the target always appeared in the same position and required subjects to make a right wrist flexion movement only of approximately 60°.

Bimanual movement training (Fig. 1b) required cursor movements to visual targets using combinations of left and right wrist flexion and extension movements. For each of the training tasks, subjects performed 160 repetitions. As shown in Fig. 1 all trials would begin with the subject bringing the cursor to a center position (X). Following this, the cursor would disappear, and a visual target would appear after a 100-ms delay. For the pre- and post-training unimanual movement trials (Fig. 1a), the target always appeared in the same position at the bottom-center of the screen as described above. For the inphase bimanual movement-training task (Fig. 1b—black target), the target appeared randomly, and at varying distances, for 160 repetitions within the top right and bottom left quadrants of the task box, along the gray diagonal line shown in Fig. 1b. Therefore, the antiphase bimanual training task required movement of antagonistic muscle representations of similar amplitudes in the two limbs. Therefore, if cursor trajectory required 30° of right wrist flexion, the left wrist was required to perform a 30° extension movement; both wrists moving simultaneously in a coordinated fashion. Repetitive unimanual training consisted of 160 repetitions to the bottom-center target location just as in the pre- and post-training unimanual movement blocks.

Two seconds following target appearance (preparation period), for all training types the cursor would reappear, and the subject was to move the cursor to the center of the target as quickly and accurately as possible. A two second delay between target presentation and cursor reappearance was chosen in order to measure cortical activity during the movement preparation period. Literature regarding the self-paced Bereitschaftspotential, a similar ERP, indicates that preparatory activity can begin up to two-seconds prior to movement onset (Deecke et al. 1969, 1987; Deecke and Lang 1996). Following a successful trial, a message would appear on the screen displaying total response time (reaction time + movement time) for that trial. Subjects had a maximum of 2 s to reach the target before the trial ended. An individual trial was deemed successful if the target was reached within 2 s. The 2 s time period was sufficient enough to allow the subject to successfully move the cursor to the target as long as initial trajectory of the cursor was accurate. Subjects were able to choose when to begin the next trial. Subjects typically rested between trials for a few seconds. The rest period was to allow subjects to blink as often as they chose, since we asked the subjects to abstain...
from blinking throughout the performance of the task to prevent the imposition of artifact into the data collection.

To assess the behavior, reaction time and movement time were recorded during each trial. Reaction time was determined as the time period between cue presentation and the beginning of cursor movement away from the center of the screen (indicated by the “X”). Movement time was determined as the time period between movement of the cursor, after cue presentation, and successful movement of the cursor to the center of the target.

Event-related potentials

Event-related potentials were extracted from the EEG by averaging individual, artifact-free epochs, time-locked to the onset of cued movement (cued movement-related potentials or MRPs), determined as the onset of EMG activity. The onset of EMG activity was manually marked and used to indicate time point zero in order to extract the MRP from the EEG recording. Prior to averaging, individual epochs containing artifacts (i.e. from blinks or muscle contractions), defined as deflections greater than 80 μV, were removed from further analysis. Averaged epochs extended from 2,000 ms prior to 1,000 ms after cued movement onset. Since the early MRP has a frequency less than 1 Hz, data were filtered with a 5 Hz low-pass filter for the quantification of early MRP amplitudes.

The early MRPs in this experiment were distributed over frontocentral electrode sites and maximal at FC3. The late MRP was lateralized and maximal over electrode site FC3. Of the 22 electrode sites recorded, MRPs were quantified at CZ, FCZ, C3 and FC3. According to the literature regarding the self-paced BP, a similar ERP to the cued MRP, these are the appropriate electrode positions used to measure the components of interest. Twenty-two electrode sites were recorded in order to have additional data for future analyses of a different nature.

The latency of the early MRP was determined as the time point when the component reached −0.2 μV from the baseline (0 μV). The amplitudes of the early MRP were quantified by calculating the mean amplitude between the range of −1,000 ms and −50 ms before movement onset (approximately 200 time points were included in the average across the chosen time range). The latency of the late MRP was determined as the peak negativity between 0 and +150 ms after the onset of movement (onset of movement occurred at time zero). Late MRP amplitudes were taken as the peak-to-peak value from the mean value calculated for the early MRP component to the peak negativity of the late MRP between 0 and +150 ms after movement onset. The re-afferent potential (RAP) amplitude was taken as the peak-to-peak value from the peak negativity of the late MRP (0 to +150 ms after movement onset) to the peak of the RAP that occurred between +200 and +350 ms after movement onset. In addition, the contingent negative variation (CNV) was quantified by averaging epochs over the 2 s foreperiod (between target presentation and the reappearance of the cursor that served as the cue to move). CNV amplitude was measured as the mean amplitude between the range of −1,000 ms and −50 ms before the presentation of the cue to move, over electrodes CZ and FCZ. Electrodes CZ and FCZ are the sites associated with the measurement of the CNV (Walter et al. 1964).

Data analysis

First, a one-way repeated measures ANOVA was used to determine that all MRP component amplitudes (early MRP, late MRP and RAP) were of similar amplitudes in the pre-training task across each training day. To test the first hypothesis that inphase BMT would induce larger cortical adaptations within regions subserving motor preparation and execution than either antiphase BMT or repetitive unimanual training, we used separate one-way repeated measures ANOVAs with training type as the factor (inphase BMT, antiphase BMT, unimanual). The dependent measures were the difference in early and late MRP amplitudes in the post-training compared to the pre-training unimanual movement tasks. A priori contrasts were used to test the specifically hypothesized differences between the training interventions. Statistical tests were performed over specific electrode positions, identified by visual inspection of the topographic distribution of the MRP, and according to the electrode positions used to assess the self-paced BP. For the pre- versus post-training unimanual movement analysis, frontocentral sites CZ, FCZ, C3 and FC3 were analyzed (CZ, FCZ for the early MRP and C3, FC3 for the late MRP). Similar analyses, excluding the a priori contrasts, were also conducted with RAP and CNV amplitudes as the dependent measures.

To test the second hypothesis that repetitive unimanual training would induce cortical activity modulations within the contralateral M1, we used one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and late MRP amplitude as the dependent measure. The third hypothesis that training-induced cortical adaptations (MRP enhancements) would be associated with enhanced performance (decrease in RT) was tested by first conducting one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and RT as the dependent measure. Secondly, the Pearson product moment correlation coefficient (r) was calculated between these measures. Specifically, post-training minus pre-training RT was plotted against post-training minus pre-training early
MRP amplitudes for the individual inphase BMT, antiphase BMT and repetitive unimanual training blocks. Prior to analysis, reaction times faster than 150 ms or that exceeded 500 ms were eliminated from further analysis. Reaction time that was less than 150 ms meant that the subject moved the cursor toward the target before the visual cue appeared and RT over 500 ms meant that the subject made an error during the task. The instance of a RT less than 150 ms or over 500 ms was rare, occurring on average 3.1 ± 0.6 times in the pre-trial and 2.9 ± 0.3 times in the posttraining trial (these averages are based upon the pre- and post-inphase trials). The eliminated RT trials were excluded from all RT analyses; the trials were not repeated and replaced with new RT data. Also, one-way repeated measures ANOVAs with time relative to unimanual movement training as the factor (pre-, post-) and movement time (MT) as the dependent measure was conducted and a second correlation analysis assessing post-training minus pre-training MT plotted against post-training minus pre-training early MRP amplitudes for the individual inphase BMT, antiphase BMT and repetitive unimanual training blocks.

To assess cortical and behavioral adaptation during skill acquisition (trial 2) for all movement-training types, early and late MRP amplitudes and RAP amplitudes were quantified from averages of the first 40 and the last 40 repetitions. Repeated measures ANOVAs with post hoc comparisons measured the first 40 versus last 40 repetitions at sites FCZ, CZ, C3, C4, FC3 and FC4. For all measures, significance was taken as $P < 0.05$.

**Results**

Pre- versus post-training unimanual movement—group analysis

The MRP consisted of three subcomponents, an early slow negativity with an onset ~1,300–1,600 ms prior to movement (early MRP), a sharper negativity beginning ~100–150 ms prior to movement onset and peaking between ~0 and 150 ms immediately following the onset of movement (late MRP). Lastly, a positive deflection, resembling the re-afferent potential (RAP) commonly observed following self-paced movement, was evident ~200–350 ms after movement onset. These MRP components are similar to the components of the Bereitschaftspotential (BP) associated with self-paced movement. The supplementary motor area (SMA), primary motor cortex (M1) and primary somatosensory cortex (S1) are the likely generators of the early, late and re-afferent components of the self-paced BP, respectively (Deecke et al. 1969; Deecke 1987; Deecke and Lang 1996).

The early MRP was maximal in amplitude and had the earliest onset over frontocentral electrode sites (greatest at FC3 (mean ± SE): $-2.44 ± 0.93 \mu V$; $-1569 ± 70 \, ms$). The late MRP peaked after movement onset (mean ± SE in ms; FCZ: 156 ± 18; CZ: 152 ± 13; C3: 143 ± 32; FC3: 126 ± 13). The scalp distribution of the late MRP was lateralized to the left hemisphere and was maximal over FC3 ($-4.48 \mu V ± 0.94$). The re-afferent potential (RAP) was maximal at CZ ($6.78 \mu V ± 1.17$) with latency occurring before 350 ms following movement onset (FCZ: 337 ± 34; CZ: 322 ± 33; C3: 303 ± 35; FC3: 259 ± 25).

There were no significant main effects of training day on pre-training early MRP amplitudes (FCZ: $F_{2,18} = 1.58$, $P = 0.23$; CZ: $F_{2,18} = 0.06$, $P = 0.94$; C3: $F_{2,18} = 0.03$, $P = 0.97$; FC3: $F_{2,18} = 0.92$, $P = 0.41$). Therefore, the amplitude of the early MRP component was comparable in the pre-training trial across each training day. There was a significant main effect of training type on early MRP amplitude post-training relative to pre-training evident at electrode site CZ ($F_{2,18} = 1.42$, $P = 0.00$). The late MRP was significant when comparing antiphase BMT and repetitive unimanual training (CZ: $F_{2,18} = 1.89$, $P = 0.17$; FC3: $F_{2,18} = 0.74$, $P = 0.48$). The contrasts revealed that this training-related difference in early MRP amplitude at CZ was due to an enhanced negativity following inphase BMT relative to the other training interventions (CZ: $F_{1,10} = 6.83$, $P = 0.02$) (Fig. 2a, b). There were no significant differences between early MRP amplitudes following BMT when comparing antiphase BMT and repetitive unimanual training (Fig. 2b).

Lastly, there were no significant main effects of training type (inphase, antiphase or repetitive unimanual) on the amplitude of either the late MRP or the RAP when comparing pre- versus post-training trials (Fig. 2a, c, d).

There were no significant group effects of training time (pre- vs. post-training) on either RT or MT following any type of training (Table 1). However, correlational analyses shown in Fig. 3 between early MRP differences and RT revealed a significant relationship between these variables such that an enhancement of early MRP amplitudes post-training was correlated with a reduction in RT but only following inphase BMT ($r = -0.77$, $P < 0.01$) and not antiphase BMT ($r = -0.46$, $P = 0.18$), or repetitive unimanual training ($r = 0.22$, $P = 0.54$). Additionally, there were no significant correlations between the early MRP differences and MT following any type of training (Table 1).

Figure 4 shows grand average contingent negative variations (CNV) derived from the pre- and post-training unimanual movement trials for each of the three types of training. There were no significant main effects of training type at either electrode site (FCZ: $F_{1,9} = 0.79$, $P = 0.39$ or CZ: $F_{1,9} = 0.83$, $P = 0.38$) when comparing the CNV in pre- versus post-training trials.
Bimanual training trial

As shown in Fig. 5 group average early MRP amplitudes significantly increased in amplitude in the last 40 repetitions compared to the first 40 repetitions of inphase bimanual movement training at sites FCZ, CZ and FC3 (FCZ: $F_{2,18} = 4.11$, $P = 0.03$; CZ: $F_{2,18} = 6.07$, $P = 0.01$; C3 $F_{2,18} = 2.15$, $P = 0.14$; C4: $F_{2,18} = 2.5$, $P = 0.11$; FC3:

Fig. 2 a Grand average MRPs ($n = 10$) time-locked to cued movement onset of the right wrist prior to (pre-training gray trace) and following (post-training black trace) practice of the inphase bimanual visuomotor training task at 4 electrode sites (FCZ, CZ, C3 and FC3). b Group mean ($±SE, n = 10$) early MRP amplitudes in the pre-training (gray bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. c Group mean ($±SE, n = 10$) late MRP amplitudes in the pre-training (gray bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. d Group mean ($±SE, n = 10$) RAP amplitudes in the pre-training (gray bars) and post-training (black bars) condition for the three types of visuomotor movement training: inphase bimanual, antiphase bimanual and repetitive unimanual. Data are shown for electrode site CZ. * Indicates $P < 0.05$. 264 × 352 mm (72 × 72 DPI)
## Table 1  Grand average early MRP amplitudes (uV) in pre- versus post-training trials at electrode sites FCZ, CZ, C3 and FC3

<table>
<thead>
<tr>
<th>Training type</th>
<th>Early MRP</th>
<th>Pre</th>
<th>Post</th>
<th>$P$</th>
<th>Pre</th>
<th>Post</th>
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<td>FCZ</td>
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<tr>
<td>In-phase BMT</td>
<td></td>
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<td>$-3.71 \pm 1$</td>
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<td>$-2.36 \pm 1$</td>
<td>$-4.8 \pm 1.1$</td>
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<td>$-3.78 \pm 0.7$</td>
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<td>In-phase BMT</td>
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<td>$244.4 \pm 23.9$</td>
<td>$225.7 \pm 24.6$</td>
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<td>$272.7 \pm 20.9$</td>
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Grand average reaction time and movement time (ms) for pre- versus post-training trials, and correlation analysis (Pearson’s r) between the post-training minus pre-training difference in early MRP amplitude in relation to reaction time and movement time for electrode site CZ.

Data are group averages (standard error).

* Indicates $P < 0.05$

$F_{2,18} = 3.49$, $P = 0.05$; FC4: $F_{2,18} = 1.1$, $P = 0.35$). Conversely, the early MRP did not change in amplitude in the last 40 repetitions compared to the first 40 repetitions of antiphase bimanual movement training or repetitive unimanual training. Task performance was not assessed in trial 2 due to task accuracy exhibiting a ceiling effect. Accuracy was based upon the subject’s ability to move the cursor into the target within 2 s following the cue to move. This time constraint was achieved frequently; therefore, a ceiling effect was encountered.

## Discussion

### Main findings

The present study assessed the usefulness of the cued MRP as a measure of cortical activation modulation in response to inphase versus antiphase BMT. Hypothesis one that cued inphase BMT, more so than cued antiphase BMT or repetitive unimanual training, would induce cortical activation modulations within regions subserving motor preparation and execution was partially supported. Practice of a novel short duration (~45 min) visually cued inphase BMT task increases preparatory activation, without an associative increase in executory activation, therefore replicating our previous findings (Smith and Staines 2006). More specifically, visuomotor adaptation, exhibited as an amplitude increase in the early MRP component (preparatory activation), in the last 40 repetitions of cued inphase BMT (Fig. 5a, b) ultimately transfers to the post-training unimanual trial (Fig. 2a, b). The late MRP component, associated with executory activation, did not change in response to cued inphase BMT (Fig. 2c). Also, alternative training strategies, such as cued antiphase BMT or repetitive cued unimanual training, did not affect any component of the MRP and therefore cortical activation (Fig. 2b, c, d). Furthermore, the contingent negative variation (CNV) (Walter et al. 1964) remained unchanged which suggests that arousal or visual cue anticipation does not contribute to the MRP modulation during or following cued inphase BMT (Fig. 4).
The second hypothesis that repetitive unimanual training would increase the amplitude of the late MRP (M1 activation) was not supported. This finding is not too surprising since the repetitive unimanual training task was simple to execute. Animal studies suggest that for learning-related plasticity to occur within M1 the task must be novel or skilled (Kleim et al. 1998; Nudo et al. 2003). Kleim et al. (1998) reported that M1 cortical representations for the wrist and digits used in a skilled task expand, whereas no change occurred in response to an unskilled movement. The pre- and post-unimanual task of the present study had to remain simple in order to elicit the MRP and to prevent introducing another learning task that would ultimately confound the purpose of the study, to assess the difference in cortical activation following inphase versus antiphase BMT, and we are satisfied that this confound was prevented.

The third hypothesis that training-induced cortical adaptations would associate with enhanced performance (decrease in RT) was supported and replicates our previous findings (Smith and Staines 2006). Enhancement of early MRP amplitude in the last 40 repetitions of inphase BMT (Fig. 5a, b) ultimately transfers to the post-unimanual trial for some participants (Fig. 2a, b). Correlation analysis reveals that enhancement of the early MRP amplitude, following inphase BMT, is significantly associated with a decrease in RT (Fig. 3a). Therefore, those participants that exhibit an enhancement of the early MRP amplitude also demonstrate a decrease in RT (Table 1). This behavioral relationship was not evident for antiphase BMT or repetitive unimanual training—paradigms that also lack a change in early MRP amplitude. Although it was not our primary objective to link cortical adaptation to behavior, the observed behavioral change provides evidence that further study is required to assess the effects of inphase BMT upon behavior.

Localization of the early MRP

Our current interest to investigate specific measurement tools to assess cortical activity modulation in response to differing modes of BMT requires the cortical localization of the measurement tool, such as the localization of the cued MRP. The presentation and topographic distribution of the cued MRP is very similar to the Bereitschaftspotential (BP), an ERP associated with the preparation and execution of a self-paced movement. The SMA, M1 and S1 primarily generate the self-paced BP, respectively; however, we cannot definitively say that the same regions generate the cued MRP. The early MRP component, observed in response to a visually cued movement—as used in the present study—may be generated by a different cortical region other than the SMA. Human (Seitz et al. 2004; Jancke et al. 2000; Koch et al. 2006; Sugita et al. 2001) and non-human primate studies (Hoshi and Tanji 2006; Riehle and Requin 1989) reveal that the preparatory stage of an externally cued movement primarily preferentially activates the dorsal portion of the lateral premotor cortex (PMd) versus the SMA that is predominantly active during the initial stages of self-generated movement. Studies of ‘virtual lesions’ to the SMA (Serrien et al. 2002; Steyvers et al. 2003) and lesion studies of the SMA (Samuel et al. 1997; Almeida et al. 2002; Almeida et al. 2003; Johnson et al. 1998; Swinnen et al. 1997) reveal that subjects can execute a unimanual or an inphase bimanual movement when the task is externally cued. However, a self-paced or antiphase task is unattainable when an SMA lesion is present. Parkinson’s patients also present with an attenuated early BP component during self-generated movement, but it remains intact during externally triggered movement (Jahanshahi et al. 1995). This evidence suggests a differential localization of the early MRP (lateral PM cortex) versus the early BP
Fig. 4 Grand average CNVs (n = 10) time-locked to the cue to move before (pre-training gray trace) and following (post-training black trace) practice of the three types of visuomotor training in 2 electrode sites (FCZ, CZ). a Inphase bimanual, b antiphase bimanual and c repetitive unimanual.

Fig. 5 a Grand average MRPs (n = 10) time-locked to cued movement onset of the right wrist in the first 40 repetitions (gray trace) versus the last 40 repetitions (black trace) of the inphase bimanual visuomotor training task (trial 2) at 6 electrode sites (FCZ, CZ, C3, C4, FC3 and FC4). b Group mean (±SE, n = 10) early MRP amplitudes in the first 40 repetitions (gray bars) and last 40 repetitions (black bars) for inphase BMT at 6 electrode sites (FCZ, CZ, C3, C4, FC3 and FC4). * Indicates P < 0.05.
(SMA), and it supports the possibility that the cued inphase BMT task used in the current study increases activation of the lateral premotor cortex, evident by the increase in the early MRP component (shown as maximal at electrode site FC3; a site overlying the lateral PM). To confirm a differential localization between the early MRP and early BP, further study is required.

Inphase BMT and cortical activation modulation

Our main finding that preparatory cortical activity increases in response to cued inphase BMT is most likely attributable to the nature of the training task. A study by Seitz et al. (2004) reported that lesions within the corpus callosum resulted in an inability to self-generate an antiphase or inphase bimanual movement; however, with a visual cue a patient can regain the ability to execute an inphase bimanual task. Data from healthy control subjects (Seitz et al. 2004) reveal that externally cued inphase bimanual movement is associated with increased activation within the lateral premotor region most likely due to an increase in activation with bilateral lateral occipital-premotor-cerebellar circuit. Seitz et al. (2004) propose that the cerebellum is the locus of bimanual coupling during externally cued inphase movement. Therefore, if the early MRP component is primarily generated by the lateral PM cortex, perhaps activation within this region increases in response to cued inphase BMT by an increase in activation within cerebellar circuits that are linked to the PM cortex. Doyon et al. (2002) demonstrate a movement-training, experience-dependent shift in cerebellar activation that increases activation within the lateral PM cortex.

Antiphase BMT and cortical adaptation

Even though the present results indicate that inphase BMT increases preparatory activity leading to a subsequent behavioral enhancement, we do not wish to discount antiphase BMT as a possible training strategy to enhance cortical activation and behavior. Differing cortical regions are predominantly active during external versus internally generated movement (Jancke et al. 2000; Koch et al. 2006; Sugiuira et al. 2001; Hoshi and Tanji 2006; Riehle and Requin 1989) and during inphase versus antiphase movement (Steyvers et al. 2003; Almeida et al. 2002, 2003; Johnson et al. 1998; Swinnen et al. 1997; Immisch et al. 2001; Sadato et al. 1997; Serrien and Brown 2002). Therefore, it is possible that antiphase BMT did not induce observable cortical activation modulations because the cue-related MRP is not an appropriate measurement tool to assess antiphase BMT modulations. Further study of the localization of the MRP versus the BP is required to understand the appropriate measurement tool to gauge cortical activity changes in response to both types of movement training.

Bimanual training and reaction time

Looking at the behavioral measure specifically, results showed that RT did not significantly change in the post-training trial of inphase BMT in the group analysis. However, it is evident in the inphase BMT correlation analysis (Fig. 3a) that some individuals exhibit an increase in the amplitude of the early MRP component with concomitant decrease in RT. Therefore, these individuals respond to the cued inphase BMT paradigm in terms of cortical activation and behavioral modulation, while other participants do not respond. Also, those participants that respond to inphase bimanual training also showed an increase in preparatory activation in the later portion (last 40 repetitions) of the inphase bimanual training trial (trial 2) (Fig. 5).

The relationship between preparatory activity (in either SMA or PMd) and RT has been demonstrated previously. In a study of Parkinson’s disease patients, Filipovic et al. (1997) reported that RT increased as SMA activity decreased. On a similar note, Di Russo et al. (2005) reported that traumatic brain injury patients who present with a decrease in medial frontal lobe activity also present with an increase in RT. Also, in a study by Mochizuki et al. (2005) a ‘virtual lesion’ to the left dorsal premotor cortex causes an increase in choice reaction time. Thus, the current results are consistent with observations that enhancement of cortical activity subserving movement preparation is associated with RT improvements.

Interindividual differences

The correlation analysis relating the difference in early MRP component amplitude and RT following cued inphase BMT (Fig. 3a) shows that some subjects do not respond to the training paradigm in terms of cortical activation modulation or behavioral enhancement. We thought that the non-responding subjects may have already produced maximal early MRP amplitudes or produced optimal RTs. However, when looking at the data, these subjects present with an averaged RT of ~280 ms in the pre-training task, whereas the average RT for the group as a whole is ~270 ms. Therefore, the non-responders were not particularly more efficient at the task in the pre-training trial. Perhaps it is more to do with the individual’s cortical recruitment strategy in that some individuals do not recruit the lateral PM region during the cued inphase task.
Conclusion

The most relevant findings of the present study are three-fold: (1) the MRP can be used to assess cortical activation modulations specifically during and following cued inphase BMT, (2) cued inphase BMT increases preparatory activation linked to enhanced behavior for a unimanual task, and (3) the cued MRP can be used as a possible measure of within session cortical activation modulations in future studies. Uncovering specific measurement tools, to assess underlying cortical activation modulation in response to specific modes of BMT, will provide the potential capability to monitor individual responsiveness to a training paradigm and can possibly lead to a methodology to assess the effectiveness of rehabilitative paradigms used in brain-injured patients.

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