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Neuromagnetic brain activity associated with anticipatory postural adjustments for bimanual load lifting

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ABSTRACT

During bimanual load lifting, the brain must anticipate the effects of unloading upon the load-bearing arm. Little is currently known about the neural networks that coordinate these *anticipatory postural adjustments*. We measured neuromagnetic brain activity with whole-head magnetoencephalography while participants performed a bimanual load-lifting task. Anticipatory adjustments were associated with reduction in biceps brachii muscle activity of the load-bearing arm and pre-movement desynchronization of the cortical beta rhythm. Beamforming analyses localized anticipatory brain activity to the precentral gyrus, basal ganglia, supplementary motor area, and thalamus, contralateral to the load-bearing arm. To our knowledge this is the first human neuroimaging study to directly investigate anticipatory postural adjustments and to explicitly partition the anticipatory and volitional aspects of brain activity in bimanual load lifting. These data contribute to our understanding of the neural systems supporting anticipatory postural adjustments in healthy adults.

Introduction

When a waiter lifts a glass from a tray of drinks balanced on one hand, his brain must rapidly solve a formidable problem of motor coordination. To maintain postural stability and avoid spilling the tray, the change in load on the load-bearing arm must be anticipated and pre-emptively countered with spatiotemporal precision (Hugon et al., 1982; Massion et al., 1999). Such *anticipatory postural adjustments* (APA) are a central feature of everyday movements but surprisingly little is known about the neural systems that support APA.

In the current study, we used magnetoencephalography (MEG) to investigate the neural mechanisms underlying APA during a bimanual load-lifting (BMLL) task. Originally developed by Hugon et al. (1982), the BMLL paradigm is essentially a simplified and experimentally controlled analogue of the waiter scenario described above.

In this paradigm, a weight is supported on one of the subject's forearms, which is then lifted using his or her other hand (*voluntary* condition). The onset of the lifting action is preceded (about 50 ms) by a relaxation of the biceps brachii muscle in the load-bearing arm, minimizing upward deflection of the forearm when the weight is unloaded (Dufosse et al., 1985; Paulignan et al., 1989). In contrast, during a control unloading (*imposed*) condition, the subject rests his/her load-lifting arm and the weight on the forearm is lifted by an experimenter. Since unloading cannot be anticipated the posture of the load-bearing forearm is destabilised, resulting in upward deflection.

Severe APA impairments observed in patients with Parkinson's disease have been taken as evidence for the critical role of the basal ganglia in generating the anticipatory response (Viallet et al., 1987). Similar impairments have also been reported in patients with lesions to the primary motor cortex (M1) and supplementary motor area [(SMA); Viallet et al., 1992]; the impairments being most pronounced when the lesion was contralateral to the load-bearing arm.

Based on these data from patients with brain lesions, Viallet et al. (1992) proposed a model to account for the coordination of movement and APA in BMLL. In their model, as motor commands are projected from M1 (contralateral to load-lifting arm) to the movement effector, a signal is also sent, via subcortical pathways, to trigger the basal ganglia, primary motor cortex, and SMA contralateral to load-bearing arm for the generation of APA.

Subsequent lesion and neuroimaging studies have also examined the role of the cerebellum in APA, but the results of these do not form a consistent picture. Diedrichsen et al. (2005) found that APA was preserved but abnormally timed in cerebellar patients performing a BMLL task via haptic interaction with a pair of robotic arms. Other studies have also reported normal APA in patients with cerebellar pathology (Mummel et al., 1998; Timmann and Horak, 2001).

Contradicting these findings, Schmitz et al. (2005) found increased cerebellar hemodynamic responses during BMLL in healthy adults, suggesting subcortical contribution to the production of APA. However, given the sluggishness of the BOLD response, it is impossible to know whether cerebellar activations took place before or after the onset of

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lifting. Thus, Schmitz et al.'s data might reflect post-movement somatosensory feedback and *not* APA.

In a recent MEG study of BMLL in healthy adults, Ng et al. (2011) reported findings that complement Viallet et al.'s model. It was noted that, during *voluntary* unloading, pre-movement brain activity was associated with event-related desynchronization (ERD) of beta-frequency (13-30 Hz) oscillations in the basal ganglia and SMA contralateral to the load-bearing arm. Additional beta ERD obtained in the contralateral thalamus led the authors to postulate that APA involves the basal ganglia-thalamo-cortical circuit that has been implicated in the preparation of motor programmes and suppression of inappropriate actions (cf. Kropotov and Etlinger, 1999).

However, a limitation of the study was that analyses were centered on the contrast between *voluntary* and *imposed* unloading. Brain activations revealed by this contrast necessarily reflect both volitional and anticipatory aspects of the task, making it impossible to isolate activity specifically associated with APA.

In the present MEG study, we employed a better control task that required the subject to lift a second weight that had been placed on a platform next to the arm bearing the first weight. In this way, the same volitional lifting action was performed in both conditions, but there was no APA component in the control task. Therefore, a contrast between the two unloading conditions should subtract out any brain activities related to volitional lifting, isolating brain activities that are specifically associated with APA.

Materials and methods

Participants

Fifteen healthy adults (8 males, 7 females; mean age 30.1, range 20–38) participated in the experiment. Fourteen of the participants were right-handed according to a modified version of the Edinburgh Handedness Inventory (Raczkowski and Kalat, 1974). Exclusion of the one left-handed participant had no effect on the pattern of results. The participants gave informed consent to the procedures, in accordance with the Declaration of Helsinki. The study was approved by the Macquarie University Human Research Ethics Committee.

Procedures

A BMLL task adapted for supine positioning was used (cf. Ng et al., 2011). Visual instructions were presented using E-Prime version 1.0 (Psychology Software Tools, Inc, Pittsburgh, US) and were projected via a mirror onto a screen, which was directly in the participant's line of sight. Throughout the experiment, the participant was instructed to fixate on a cross on the screen to minimize eye-movement artefacts and to ensure that they were not watching the lifting action. Compliance with fixation was continuously monitored during the session by the experimenter. Off-line examination of MEG data confirmed compliance, with few or no trials being rejected for eye-movement artefact. The participant's load-bearing (left) arm was positioned adjacent to the trunk so that elbow flexion could be performed comfortably. In order to minimize movements at the left shoulder joint, the upper arm was taped to a support placed proximal to the elbow joint. The left hand rested on a support placed near the wrist joint such that the forearm was inclined about 15 degrees from the horizontal plane. A 12 cm×12 cm platform was secured to the load-bearing arm, just above the wrist.

During BMLL, the participant used his or her right hand to lift the weight off the platform on the left arm. In the *control* task, the weight remained on the participant's left arm and he or she lifted a second identical weight from another platform placed adjacent to the load-bearing arm (Fig. 1a). The two conditions were, therefore, equated for both the pre-lifting proprioceptive experience and the unloading movement completed by the right arm. Thus, any differences in brain activity between the two tasks immediately preceding the onset of lifting should equate to the APA response.

At the start of a trial, the participant fixated on a white cross. A visual stimulus 'R' (i.e. Ready), below the cross, cued the participant to raise the load-bearing arm to an angle approximately 20 degrees from the horizontal plane. The experimenter then placed a 700-g weight on the wrist platform and the participant positioned the load-lifting right hand (with an appropriate grip aperture) near the to-be-lifted weight. Once the hand was positioned, the experimenter pressed a key to initiate a cue (change of fixation cross from white to red) for the participant to get ready to lift the weight. When the red cross disappeared from the screen, the weight was to be lifted voluntarily (Fig. 1b).

Immediately after BMLL and control unloading, the experimenter retrieved the weight from the participant's right hand. In the control task, the weight on the participant's load-bearing arm was *not* lifted as part of the trial; the experimenter only unloaded the weight to mark the end of a trial.

A total of 70 trials (2 blocks of 35 trials) per condition were performed and the order of trials was counterbalanced between participants.

Data acquisition

Unloading forces were sampled at 1 kHz using a fiber-optic force sensor (MAG Design & Engineering; Redwood City, CA) placed underneath the to-be-lifted weight. Electromyography (EMG) activity was also sampled at 1 kHz using MEG-compatible surface electrodes (BrainProducts, Gilching, Germany). During the trials, EMG activity was recorded from two muscles contributing to the elbow joint torque of the load-bearing arm: biceps brachii and triceps brachii. Force and EMG signals were amplified and band-pass filtered between 20 and 450 Hz.

Brain activity was recorded with a whole-head MEG system (Model PQ1160R-N2, KIT, Kanazawa, Japan) consisting of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003). Prior to MEG measurements, five marker coils were placed on the participant's head and their positions and the participant's head shape were measured with a pen digitiser (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing the marker coils in the MEG dewar immediately before and after the recording session. Movement tolerance was set at a threshold of 5 mm for any individual coil. MEG was sampled at 1 kHz and band-pass filtered between DC and 200 Hz.

T1-weighted, 3-D structural scans were obtained from all participants in a separate session using either a 3 T Phillips Achieva MRI scanner at St Vincent's Hospital, Darlinghurst, NSW, Australia or a 3 T Siemens Verio MRI scanner at Macquarie University Hospital, Marsfield, NSW, Australia. Scans were 1 mm isotropic.

Data analysis

Force and EMG analyses

The onset of unloading ($t=0$) was defined as the point of first decrease in force on the force meter, as determined by a threshold-crossing algorithm (DiFabio, 1987). EMG data 400 ms preceding and 800 ms following the onset of loading were grouped by condition, rectified, and averaged across trials for each participant. The latency of the first downward deflection in biceps brachii EMG (i.e. onset of inhibition) was determined using a similar algorithm. Paired-samples *t*-test compared within-condition differences in biceps brachii and triceps brachii EMG amplitude from −400 to −100 ms. A separate paired-samples *t*-test evaluated within-subject differences in biceps brachii EMG amplitude in the same time period in both unloading conditions.

MEG analyses

MEG analyses were centered on the beta (15–30 Hz) frequency band, a cortical rhythm that is closely related to motor behaviours (Pfurtscheller and Lopes da Silva, 1999; Taniguchi et al., 2000). MEG

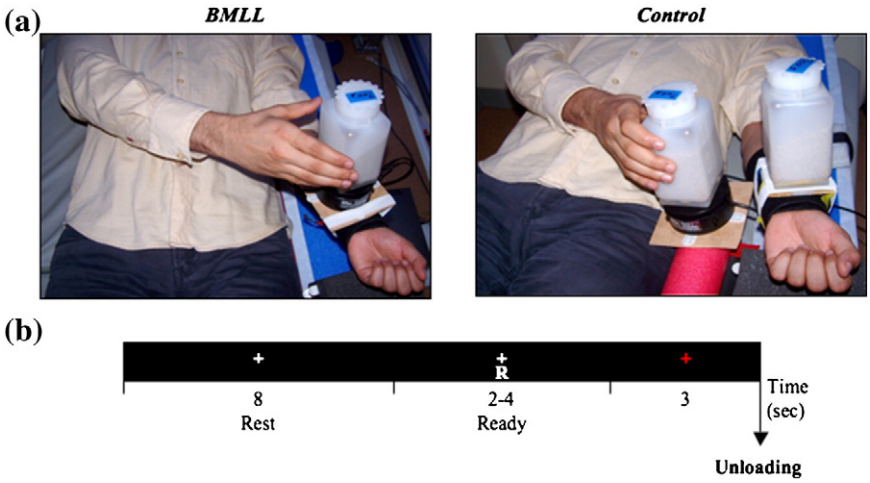

Fig. 1. (a) Unloading conditions. During *BMLL*, the participant lifted a 700-g weight off the force sensor on the load-bearing arm with the contralateral hand (*left*). During the *control* task, the participant supported the same 700-g weight on the load-bearing arm but lifted an identical weight off the force sensor, which was secured to a support platform placed between the load-bearing arm and the trunk (*right*). (b) Timing of visual cues during a trial.

signals were downsampled to 250 Hz, concatenated, and lowpass filtered at 45 Hz. Signals within an epoch 1500 ms preceding and 4000 ms following the onset of unloading were analyzed using SPM8 (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK, www.fil.ion.ucl.ac.uk/spm). Artefacts including blinks and eye-movements were removed using the artefact rejection tool implemented in SPM8. The MEG coordinate system was transformed into the Montreal Neurological Institute (MNI) coordinate system.

Sensor space analysis

Modulations of source power for all MEG sensors were obtained from single trial data (−1500 to 4000 ms) using multitaper functions with a sliding time window of 1000 ms and a time bin of 50 ms. Source power maps were log10 transformed, averaged across all trials over a frequency band 6 to 40 Hz, and smoothed using a Gaussian kernel [full-width half-maximum (FWHM), 15 mm] (Kilner and Friston, 2010; Litvak et al., 2011). From the grand mean time-frequency representation (TFR) plots, sensors (one in each hemisphere) that showed the greatest beta ERD were selected for further analysis. The voxel with the strongest beta desynchronization prior to unloading was identified from the grand mean TFR plots and group statistical analyses for beta source power modulation were carried out based on the peak frequency and latency of this voxel. Paired-samples t-tests compared differences in beta source power across conditions.

Source analysis

A canonical cortical mesh derived from the MNI template was warped, in a nonlinear manner, to match the participant's structural MRI scan. Based on a single shell model, the ensuing mesh was entered into a forward model computation of the source lead fields. Using a beamformer approach, each individual forward model was inverted to localize sources in a common stereotactic space (Litvak et al., 2011; Mattout et al., 2007). Source localization was carried out using linearly constrained minimum variance beamformers. This approach optimizes the weight of the beamformer to capture the signal of interest while concomitantly minimizing interfering signals and noise approaching from other directions (Van Veen and Buckley, 1988). In the current study, beamforming analyses were performed on a 400 ms time window immediately preceding the onset of unloading in both conditions (see Fig. 2). Independent beamformers constructed for each location in brain space resulted in a 3D estimate of source power, which was normalized to a baseline 3600 to 4000 ms after the onset of unloading when the arms had returned to the resting position. This was at least three seconds after the experimenter had unloaded weights from both arms. For each unloading condition, beamforming analyses yielded a 2 mm resolution *'CON'* image for each participant.

Group inferences for task-baseline (*BMLL-baseline*, *Control-baseline*) and between-task (*BMLL-control*) brain activations were carried out using random effect analyses. *'CON'* images from the participants were grouped by condition. Brain activations prior to *BMLL* were contrasted with those in the same time period during the *control* task to reveal brain activations that were specifically associated with APA. Based on the previous literature, regions of interest (ROI) were defined in the basal ganglia (see Viallet et al., 1987), SMA (see Viallet et al., 1992), thalamus (see Ng et al., 2011), and cerebellum (see Schmitz et al., 2005) using the WFU Pickatlas (Maldjian et al., 2004). A 3D space defined by a 20×20×20 mm box containing the maxima identified from the contrast *T* map were subjected to small volume correction (Worsley et al., 1996). Only sources that survived family-wise error rate (FWER) correction with significance level set at $P<0.05$ were reported. Activations were superimposed onto a MNI template brain, and their anatomical labels were determined using xjView 8 (http://www.alivelearn.net/xjview8).

Results

Force data

Across participants, no significant (t (14) = 1.14, $P = 0.28$) differences were found between the onset of *BMLL* (M = 3.23 seconds, SD = 0.19 seconds) and *control* (M = 3.29 seconds, SD = 0.08 seconds) unloading following the presentation of the visual stimulus.

EMG measurement

Fig. 2 shows biceps brachii and triceps brachii EMG recorded from the load-bearing arm of a representative participant. During BMLL, the onset of biceps brachii EMG inhibition was 52 ms prior to the onset of unloading. Across participants, biceps brachii EMG inhibition started 56.97 ± 17.36 ms (Mean ± SD) prior to unloading. This onset latency agrees well with those previously reported, that is, 30 to 70 ms preceding the onset of unloading (Hugon et al., 1982). In contrast, prior to unloading in the *control* task, no significant changes in biceps brachii EMG was observed, as the postural left arm was unperturbed by the unloading movement (see Fig. 1a).

From −400 to −100 ms prior to BMLL, grand mean EMG amplitude was significantly (t (14) = 7.15, $P<0.001$) greater in the biceps brachii (M = 11.40 microvolts, SD = 5.68 microvolts) compared to the triceps

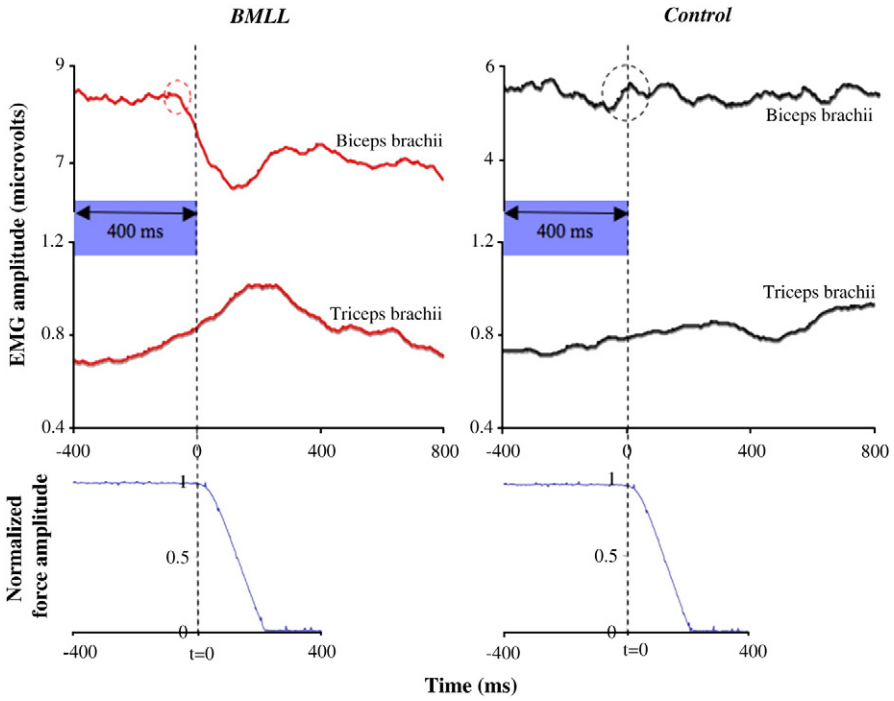

Fig. 2. EMG measurements for a representative participant. The first decrease in normalized force amplitude was taken to represent the onset of unloading [($t=0$); *bottom*]. During *BMLL*, biceps brachii EMG in the load-bearing arm started to decrease at −52 ms (*red* circle). In contrast, no decrease in biceps brachii EMG was observed immediately before or after the *control* task (*black* circle). A 400 ms time window preceding the onset of unloading (*blue* box) was used for subsequent MEG analyses.

brachii (M = 2.28 microvolts, SD = 0.93 microvolts). Similarly, in the same time period prior to control unloading, grand mean EMG amplitude was significantly (t (14) = 9.17, $P<0.001$) greater in the biceps brachii (M = 10.91 microvolts, SD = 4.37 microvolts) compared to the triceps brachii (M = 2.00 microvolts, SD = 0.81 microvolts).

In the same time period, individual *t*-test showed that, in *all* the subjects, biceps brachii EMG amplitude was significantly greater prior to BMLL compared to control unloading.

MEG measurement

Sensor space analysis

Fig. 3(a) shows scalp topography of grand mean source power maps during unloading. Fig. 3(b) shows grand mean source power maps of two MEG sensors in the proximity of the left and right sensorimotor cortices. Over the left sensorimotor cortex, volitional movements of the right hand elicited robust beta desynchronization that was prominent during *BMLL* and the *control* task. In contrast, over the right sensorimotor cortex, robust beta desynchronization was observed only prior to *BMLL*. There was no significant (t (14) = −0.58, $P=0.57$) right hemisphere beta desynchronization prior to unloading in the *control* task. These results provide a clear confirmation, at the sensor level, that beta ERDs reflect the pattern of activation of left and right hemispheric motor cortices expected from our experimental manipulations and are consistent with the EMG results.

Source analysis

The contrast between BMLL and its baseline epoch showed significant beta ERD in the medial region of the left precentral gyrus, consistent with the expected activation of the hand/arm area during this task (Table 1). The same region showed beta ERD for the contrast between the control task and its baseline. These results confirm that the volitional movements of the right arm of both tasks engaged common areas of the contralateral left precentral gyrus. In other words, the volitional aspects of both tasks were well equated.

On the other hand, a direct contrast between the *BMLL* and *control* tasks revealed sources that were right lateralized (i.e., contralateral to the load-bearing arm). Table 2 and Fig. 4 show statistically significant beta ERDs obtained in the right SMA, basal ganglia, and thalamus. There were no significant task-related ERD differences in any regions of the left hemisphere.

Apart from these sources, one other brain region in the right hemisphere showed robust beta ERD. Fig. 5 shows statistically significant beta ERDs in the right precentral gyri including a region in the lateral aspect of Brodmann area (BA) 6.

Discussion

The current study represents, to our knowledge, the first evidence from healthy adults pertaining to the neural mechanisms of APA. By contrasting oscillatory brain activity in a BMLL task with a control condition that involved the same volitional movement, we were able to isolate brain regions specifically involved in APA. Regions thus identified included the basal ganglia, thalamus, and SMA contralateral to the load-bearing arm. In addition, significant beta source was also obtained in the right precentral gyrus including a region in the lateral aspects of Brodmann Area 6. There was, however, no evidence for cerebellar involvement in APA.

Beta ERD in sensor space

During BMLL and control unloading, lifting movement performed by the right hand elicited robust beta ERD that was observed over the left sensorimotor cortex. The timing of this ERD agrees well with the onset latency of premovement ERD in self-initiated movements (Derambure et al., 1993; Pfurtscheller and Berghold, 1989; Stancak and Pfurtscheller, 1996). In these studies, a homologous ERD starting immediately before

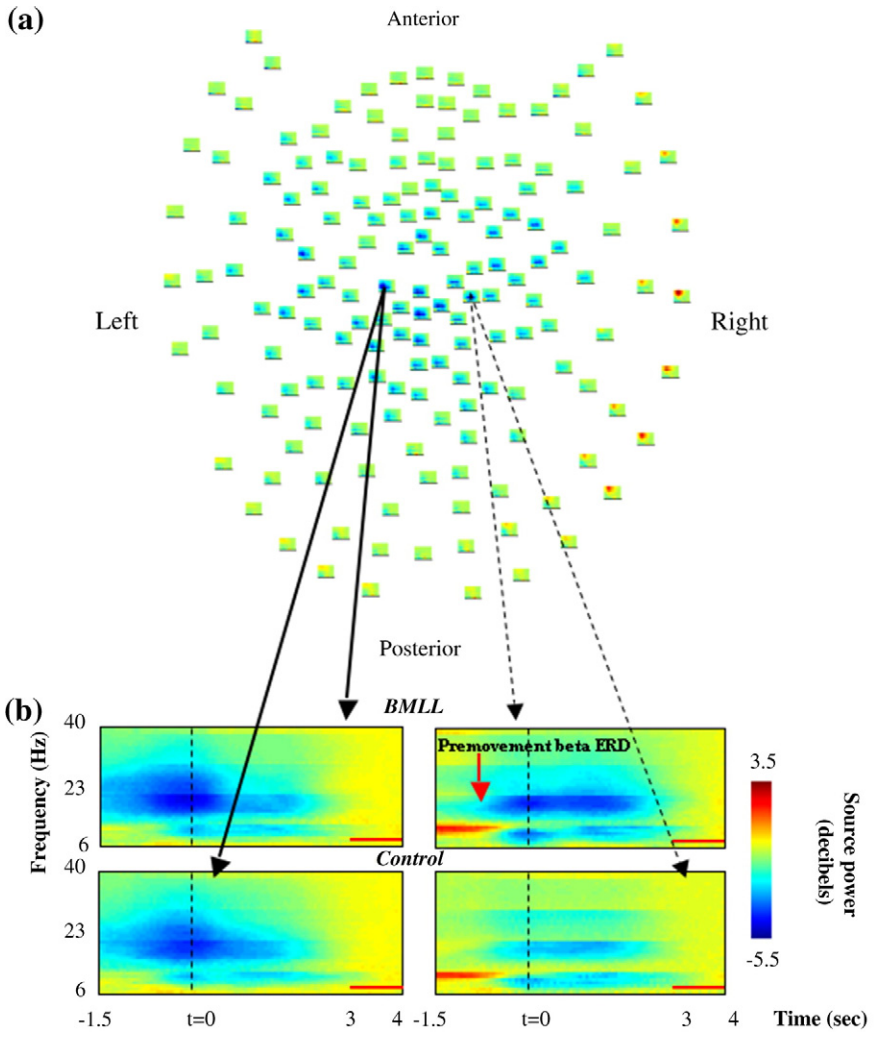

Fig. 3. (a) Scalp topography of grand mean source power maps. (b) Grand mean source power maps recorded at two sensors over the left (*bold* arrows) and right (*dotted* arrows) sensorimotor regions during *BMLL* and the *control* task. Modulation of source power was normalized to a baseline (*red* lines) after the onset of unloading. Over the right sensorimotor cortex, premovement beta ERD was observed only prior to *BMLL* (*red* arrow).

movement was also observed over the right sensorimotor cortex. Interestingly, in the current study, beta ERD over the right sensorimotor cortex did not start immediately but about 800 ms before movement (see Fig. 3b, top right plot). We postulate that this ERD was not an epiphenomenon of volitional movement, nor reflected brain activations for supporting the weight as the same ERD was not observed during the control task (see Fig. 3b, bottom right plot). It is likely that the beta ERD observed over the right sensorimotor cortex in BMLL was related to the control of APA. In a recent EEG study of BMLL, Barlaam et al. (2011) showed that mu rhythm desynchronization over the same brain region was associated with APA. Further work is needed to evaluate the role of mu and beta ERD in the generation of APA.

Table 1
MNI coordinates and anatomical labels of FWER-corrected brain sources thresholded at T > 8.25 as revealed by task-baseline contrast.

Brain region	*T* value	*P* value	Coordinates (mm)		
			x	*y*	*z*
BMLL-Baseline					
Frontal lobe					
Precentral gyrus	8.26	<0.01	−38	−18	56
Control-Baseline					
Frontal lobe					
Precentral gyrus	10.19	<0.01	−34	−30	62

Table 2
MNI coordinates and anatomical labels of FWER-corrected brain sources thresholded at T > 2.72 as revealed by between-task contrast.

Brain region	*T* value	*P* value	Coordinates (mm)		
			x	*y*	*z*
Frontal lobe					
Precentral gyrus/BA 6	5.72	<0.01	56	−8	36
Precentral gyrus	5.52	0.01	52	−8	26
Precentral gyrus/SMA[a]	3.25	0.02	14	−20	68
Sub-gyral/SMA[a]	3.24	0.02	12	−20	62
Medial frontal gyrus/SMA[a]	3.07	0.03	8	−20	56
Sub-lobar					
Basal ganglia					
Lentiform nucleus/putamen[a]	3.56	0.01	28	−16	−2
Extra-nuclear/putamen[a]	3.54	0.02	34	−12	4
Caudate/caudate head[a]	3.34	0.02	6	8	−4
Lentiform nucleus/lateral globus pallidus[a]	2.89	0.03	22	−12	2
Extra-nuclear/thalamus[a]	2.73	0.04	18	−12	4

[a] Significant sources after small volume correction.

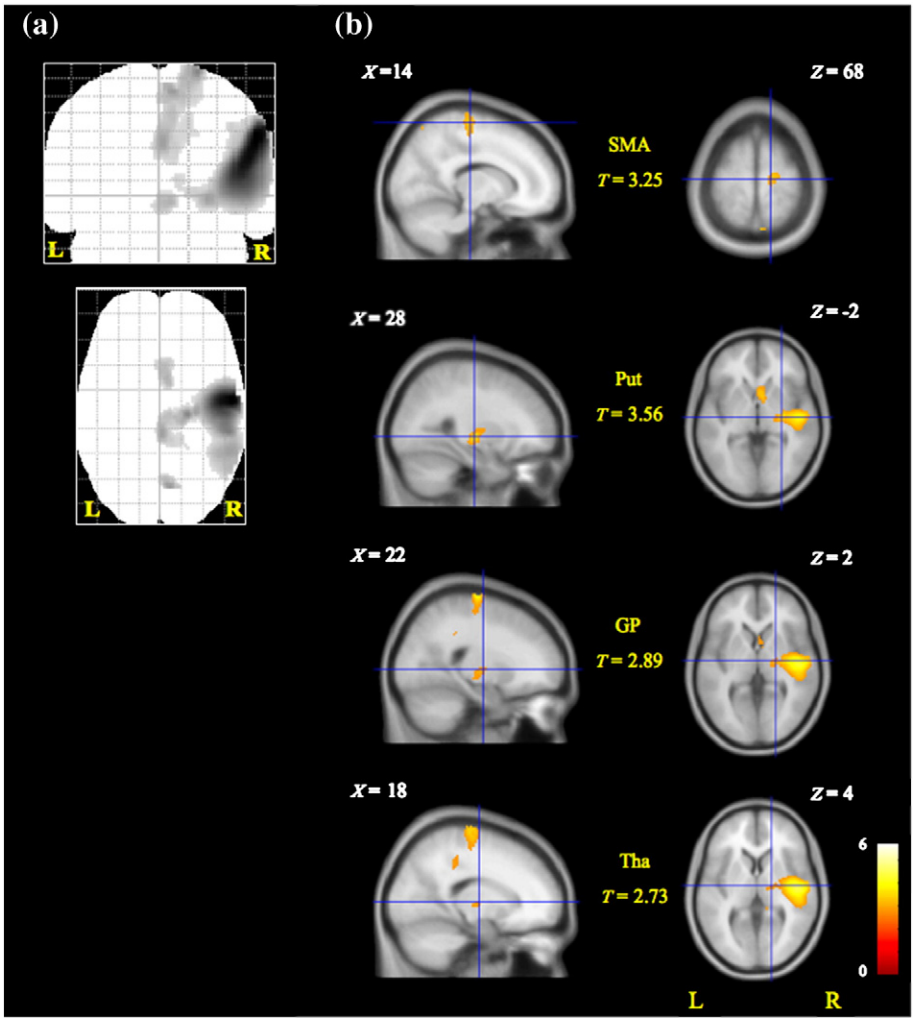

Fig. 4. (a) APA-related activations, as shown in the template glass brain. (b) Location of beta sources constituting the canonical basal ganglia-thalamo-cortical network in the hemisphere contralateral to the load-bearing arm. SMA — supplementary motor area. Put — putamen. Tha — thalamus. All FWER-corrected maps are thresholded at $T > 2.72$.

Beta ERD in source space

Beamforming analyses performed on a premovement epoch 400 ms preceding the onset of unloading revealed significant desynchronization of beta-frequency oscillations in the right SMA and three specific components of the basal ganglia; the putamen, caudate, and globus pallidus. These findings are consistent with our previous MEG results. Crucially, we are now able to confirm that the involvement of these brain regions in BMLL is specifically related to the APA component of pre-movement brain activity. The current data also concur with findings of impaired APA in patients with Parkinson's disease or lesions involving the SMA (Viallet et al., 1987, 1992). Together, they provide converging evidence that the basal ganglia, SMA, and thalamus play a critical role in the central organization of APA (cf. Viallet et al., 1992).

These brain regions represent component nodes of the canonical basal ganglia-thalamo-cortical 'motor' network (Alexander et al., 1986, 1990). In this network, the putamen receives extensive cortical input from the motor and somatosensory cortices, premotor areas, and SMA (Alexander and Crutcher, 1990; Brooks, 1995) and connects to the thalamus (Devito and Anderson, 1982; Illinsky et al., 1985) via the globus pallidus (Johnson and Rosvold, 1971; Parent et al., 1984). In turn, the thalamus projects back to a number of motor areas including the SMA (Schell and Strick, 1984; Strick, 1976; Wiesendanger and Wiesendanger, 1985).

A number of studies have implicated the motor network in the selection and preparation of motor programmes (Deiber et al., 1991; Tanji and Shima, 1994) and the suppression of inappropriate actions before implementation (Kita, 1994; Marsden and Obeso, 1994; Mink and Thach, 1991; Wichmann and DeLong, 1994). More recently, findings from neuroimaging studies suggest a central role in the implementation of well-learned movements. Using positron emission tomography, Boecker et al. (1998) found widespread activation of the motor-, premotor-, and parietal cortical areas, along with basal ganglia and thalamus during performance of well-learned, sequential finger movements. Using functional magnetic resonance imaging (fMRI), Doyon et al. (2002) also found significant activations of the striatum, SMA, and cortical association areas during advanced stages of learning a motor sequence. Given that APA is well learned and automatic in adults (Schmitz et al., 2002), the current results suggest that this canonical network may also be involved in the mediation of APA.

In addition to the basal ganglia, SMA, and thalamus, we also observed beta ERD in the lateral aspects of the right precentral gyrus, a region of the brain commonly referred to as the ventral premotor cortex (vPM). The functional role of the vPM in APA is not well established. Findings from primate and human studies suggest that the brain region is involved in coding locations of somatosensory (visual, auditory, and tactile) stimuli in extrapersonal space with respect to a body-centered reference frame (Fogassi et al., 1996; Galati et al., 2001). It is believed that the formation of spatial maps in the brain enhances perception of limb position, which in turn guides volitional movements (Graziano and Gross, 1998; Graziano et al., 1997; Rizzolatti et al., 2002). On the basis of these findings, the observed activation of the vPM may be related to spatial coding of tactile information necessary for determining the postural

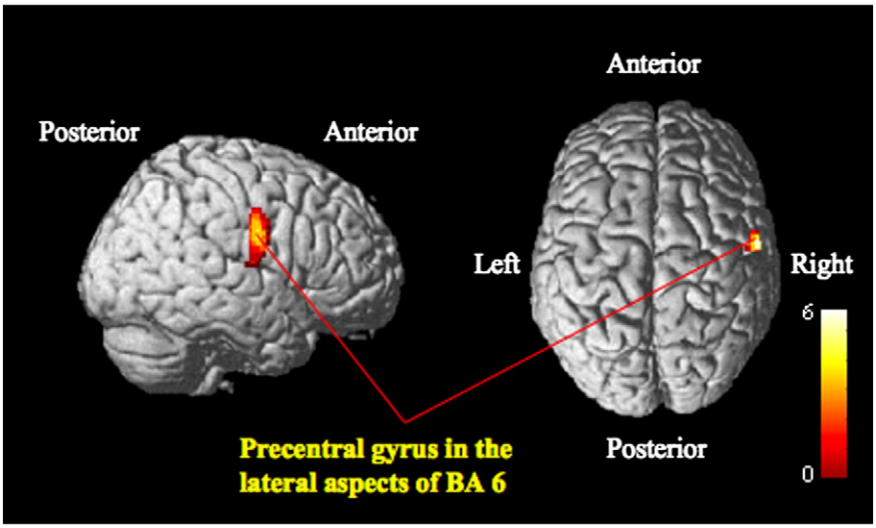

Fig. 5. Grand mean beta source images revealed by the *BMLL-control* contrast, superimposed on a MNI rendered brain. The color bar refers to source power modulation expressed in *T* values.

forearm reference position, thought to be a prerequisite for coordinated control of volitional and anticipatory motor actions in BMLL (Massion et al., 1998, 1999).

Cerebellum and its role in APA

In the current study, we did not find any evidence of cerebellar involvement in APA. A potential argument here is that MEG systems are simply incapable of picking up cerebellar activity. However, a number of neuromagnetic studies have demonstrated significant cerebellar activations during motor tasks (e.g. Gross et al., 2002; Jerbi et al., 2007). Furthermore, there is evidence that neurons in the cerebellum do oscillate at the beta frequency band, in sync with those in the thalamus and cortical motor areas to sustain processes related to motor control (Brown, 2007; Jenkinson and Brown, 2011; Schnitzler and Gross, 2005).

This null result contradicts the findings of an earlier fMRI study by Schmitz et al. (2005) showing that BMLL is associated with increased cerebellar hemodynamic response. Given the temporal resolution of fMRI in the order of seconds (Kim et al., 1997; Ogawa et al., 1990), it is impossible to differentiate between neural activity occurring before or after movement onset. It is possible, therefore, that cerebellar activations observed by Schmitz et al. (2005) reflected post-movement sensory feedback (cf. Jueptner and Weiller, 1998) rather than any premovement anticipatory responses.

The role of the cerebellum in bimanual coordination is not well understood. As noted earlier, APA is preserved in patients with cerebellar lesion or pathology. However, there is some evidence that APA is less synchronized to movement onset in these patients, suggesting that the cerebellum may be involved in the temporal organization of the anticipatory response (Babin-Ratte et al., 1999; Diedrichsen et al., 2005; Diener et al., 1989).

The cerebellum has also been implicated in motor learning as a module for computing sensory errors arising from a mismatch between an intended motor plan and the actual motor outcome (Imamizu et al., 2000; Kawato, 1999; Wolpert et al., 1998). On this view, damage to the cerebellum would severely impair sensorimotor integration and subsequently motor learning. Indeed, Diedrichsen et al. (2005) found that, although APA for well-learned movements was intact in patients with cerebellar damage, they failed to acquire APA for a novel bimanual coordination action in which mechanical lifting from one arm was triggered by the participant pressing a button with the other hand.

Cerebellum and PPC involvement in sensorimotor control

Functional interaction between the cerebellum and posterior parietal cortex (PPC) has also been implicated in sensorimotor control. In a recent MEG study (Pollok et al., 2008) , participants learned to synchronize finger-tapping movements to sequentially presented tones. Based on a combination of sensory reafferents and active representation in working memory, the participants could alter the rate of movements during an ongoing trial to minimize errors. The PPC, in particular, has been implicated in such sensory-driven processes (Andersen et al., 1997; Cohen and Andersen, 2002).

Data from humans (Della-Maggiore et al., 2004; Desmurget et al., 1999) and primates (Mulliken et al., 2008) engaged in rapid trajectory movement support such as a role of the PPC. For example, in the latter study, duration of a movement trajectory could last up to 450 ms. It is possible that, at the later stages of the trajectory, even sensory signals with large (70 ms) time delays (Kawato et al., 2003) could be utilized for motor control and error correction (Mulliken et al., 2008). However, this type of sensorimotor control cannot be applied to APA, as the duration of the anticipatory response is too brief for any sensory information to be useful for error correction.

Cerebellum and PPC involvement in precision grip-lift task

Another type of motor action with anticipatory processes that closely resemble APA in BMLL is the precision grip-lift task. Much like the BMLL task where biceps EMG modulation precedes the destabilizing unloading forces; in the grip-lift task, changes in grip force precede and mirror changes in load force to prevent slippages (Flanagan and Tresilian, 1994; Blakemore and Sirigu, 2003; Blakemore et al., 1998). These anticipatory responses (APA and predictive grip force modulation), unlike those reported in Pollok et al.'s (2008) and other studies (Della-Maggiore et al., 2004; Desmurget et al., 1999; Mulliken et al., 2008), are discrete, meaning that each elicited response is specific for counteracting only the forthcoming destabilizing force. Furthermore, given that destabilizing forces vary randomly from trial to trial in BMLL (Hugon et al., 1982) and during movement in grip-lift tasks (Flanagan and Wing, 1993, 1997; Flanagan et al., 1993), it is highly unlikely that sensory information from one trial is utilised for counteracting destabilizing forces in subsequent trials. On the basis that APA and grip force modulation are elicited before the destabilizing

forces suggests that these anticipatory responses are an integral component of the motor planning process.

This conjecture is consistent with the view that a forward internal model that predicts action consequences from efference motor plans is needed for the coordination of predictive grip with load (Kawato et al., 2003). The authors posited that the cerebellum might be the site that contains the forward internal module. A number of neuroimaging studies have since demonstrated significant cerebellar activations specific to grip-load coupling (Boecker et al., 2005; Ehrsson et al., 2003). Additionally, Ehrsson et al. (2003) showed that the human PPC is also crucially involved in the predictive control of grip force with load.

Given the likeness of the anticipatory response in BMLL and the grip-load task, it is not clear why, in the current study, beta ERD was not obtained in the cerebellum and PPC. A couple of explanations are plausible. First, in the above block-design fMRI and PET studies, *pre*- and *post*-movement brain activity were taken into account for the between-task analyzes to isolate brain regions underlying grip-load coupling. However, due to the poor temporal resolution of these modalities, the observed cerebellar and PPC activations could reflect either processes related to anticipatory grip force or post-movement sensory integration. Second, the anticipatory and volitional component of the grip-load task is constrained to one limb, whereas those same components in BMLL require bimanual coordination. Future work is needed to clarify the contribution of the cerebellum and PPC in the generation of APA.

Limitations of the study

A number of factors have to be considered when interpreting data from the present study. First, it is possible that differences in biceps brachii EMG prior to BMLL and control unloading could contribute to differences in scalp-recorded MEG signals. These differences arose because in BMLL, the postural forearm supported the force sensor (about 300 g), platform, and weight; whereas, in control unloading, it only supported the platform and weight. Such differences in joint torque EMG have been shown to be controlled primarily by contralateral brain structures (Colebatch et al., 1991; Wexler et al., 1997). Specifically, the primary motor (Sehm et al., 2010) and sensorimotor (Liu et al., 2003) cortices have been implicated in the modulation of joint torques in distal muscles. On the basis that beta ERD was not obtained in the right M1 or sensorimotor cortex suggests that the current differences in biceps brachii EMG across conditions were marginal. Furthermore, it is highly unlikely that the basal ganglia-thalamo-cortical network reported in the current study was related to the control of muscle force production.

Second, an ongoing debate concerning MEG is that the modality cannot detect sufficiently well signals in brain structures remote from the recording sensors. One example is the cerebellum, which lies in subcortical brain space inferior to the occipital and temporal neocortices. Nevertheless, a part of the structure, the posterior cerebellum, lies close to the skull. Perhaps, it is due to this proximity between the cerebellar cells and MEG sensors that enables consistent recording and localization of cerebellar activity (Gross et al., 2002; Martin et al., 2006; Pollok et al., 2008; Tesche and Karhu, 1997).

In contrast, localization of signals from the basal ganglia and thalamus are more problematic, as they lie deep in subcortical brain space and are entirely surrounded by the neocortices. Given their anatomical locations, it is difficult to record reliably activity from these structures, as the signals tend to be weaker and/or noisier, which in turn, affect the accuracy of source localization (Hari et al., 1988). A number of studies have encountered this problem and referred the basal ganglia and thalamic activity as diencephalic (Pollok et al., 2008; Timmermann et al., 2003).

However, a number of MEG studies have been able to differentiate activations between the thalamus and basal ganglia; even between distinct nuclei of the basal ganglia (e.g. Fujioka et al., 2010, 2012). In the current analysis, although we reported activations in the putamen, caudate, and globus pallidus, it is important to note that these sources were not significant at a thresholded whole brain level; they were significant only after ROI analyses and small volume correction. We speculate that it is the combination of the beamformer, ROI analyses, and small volume correction that enabled us to resolve spatial resolution in the basal ganglia. Future work is needed to test this hypothesis and evaluate subcortical contribution to APA in BMLL.

Conclusions

Our findings obtained with healthy adults showing significant beta ERDs in the basal ganglia, SMA, and thalamus in the hemisphere contralateral to the load-bearing arm are consistent with the lesion-based APA model of Viallet et al. (1992). Of particular interest is that these brain areas are component nodes of the canonical basal ganglia-thalamo-cortical motor network, which has been implicated in well-learned, automatic movements. We posit that this network is involved in the mediation of APA. Further work is needed to infer the effective connectivity of the motor network. Such studies will enhance our understanding of the neural mechanisms of motor coordination in healthy humans.

Disclosure statement

The authors report no conflict of interest.

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