The Excitability of Ipsilateral Motor Evoked Potentials Is Not Task-specific and Spatially Distinct From the Contralateral Motor Hotspot

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Abstract

Objective

The role of ipsilateral descending motor pathways in voluntary movement of humans is still a matter of debate. Few studies have examined the task dependent modulation of ipsilateral motor evoked potentials (iMEPs). Here, we determined the location of upper limb biceps brachii (BB) representation within the ipsilateral primary motor cortex.

Methods

MR-navigated transcranial magnetic stimulation mapping of the dominant hemisphere was undertaken with twenty healthy participants who made tonic unilateral, bilateral homologous or bilateral antagonistic elbow flexion-extension voluntary contractions. Map center of gravity (CoG) and area for each BB were obtained.

Results

The map CoG of the ipsilateral BB was located more anterior-laterally than those of the contralateral BB within the primary motor cortex. However different tasks had no effect on either the iMEP CoG location or the size.

Conclusion

Our data suggests that ipsilateral and contralateral MEP might originate in distinct adjacent neural populations in the primary motor cortex, independent of task dependence.

1. Introduction

For a long time, it was assumed that voluntary limb movements were executed exclusively by the contralateral primary motor cortex. In recent decades, several studies have found that the ipsilateral primary and premotor cortices are also activated during the coordination of bimanual movements and for maintaining posture (Bundy & Leuthardt, 2019). These ipsilateral motor cortical areas are also recruited to compensate for congenital or acquired brain injury (Staudt et al., 2002; Bradnam et al., 2013).

The recruitment of ipsilateral motor pathways can be examined neurophysiologically with transcranial magnetic stimulation (TMS) (Armand and Kuypers, 1980; Wassermann et al., 1994; Ziemann et al., 1999). Ipsilateral motor evoked potentials (iMEP) are distinct the contralateral MEPs (cMEP) in a few important ways. They tend to have a later onset, a higher threshold and smaller size, indicating a weaker and possibly indirect route to the spinal alpha motor neurons. Furthermore, iMEPs can been obtained more readily in proximal compared to distal muscles (Bawa et al., 2004; Wassermann et al., 1994) and are usually only present when the target muscle is pre-activated (Bawa et al., 2004; Chen et al., 2003). These characteristics reinforce their potential importance for bimanual or postural motor interaction.

Tazoe and colleagues also described a task dependence of iMEP excitability (Tazoe and Perez, 2014). In their study, iMEPs obtained from the non-dominant biceps brachii (BB) were smaller during contraction of both BB compared to unilateral, non-dominant BB activation. In addition, heterologous bilateral movements, which required contraction of the non-dominant BB with coincident contraction of the dominant triceps brachii, revealed the largest iMEPs compared to task contexts. The authors speculated this was due to a modulatory influence of interhemispheric inhibition (Perez et al., 2014) and neck afferent inputs (Tazoe and Perez, 2014).

Another explanation for a task related difference in iMEPs could relate, at least in part, to a task-dependency of the cortical iMEP representation, captured by the “hotspot”. Most commonly, the hotspot for the contralateral MEP is assumed to be the hotspot for the iMEP (Chen et al., 2003; McCambridge et al., 2016; Tazoe and Perez, 2014). An alternative approach is to calculate a center of gravity (CoG) from a grid of scalp locations, as has been done in somatotopic investigations (Lotze et al., 2003). However, only a few iMEP studies used CoG for describing the location of the iMEP. Ziemann et al. (1999) found a lateral and anterior shift of the CoG of the first dorsal interosseous (FDI) representation in seven participants during unilateral tonic contraction compared to the cMEP hotspot. In contrast, the CoG of the BB iMEP was more medial and anterior during tonic unilateral contraction in the 16 participants examined by Tazoe (2014). Furthermore, a difference was found between FDI iMEPs and proximal deltoid in seven participants studied by Wasserman and colleagues (Wassermann et al., 1994). During tonic unilateral contraction, FDI iMEPs were elicited for a hotspot that was more lateral, and deltoid iMEPs from a hotspot that was more medial compared to cMEPs. In most cases iMEP hotspots exhibit greater variability between participants than those used to obtain cMEPs. Methodological differences between studies, low sample sizes, different movement contexts and means of establishing locations of stimulation preclude a more definitive interpretation about iMEP hotspot characterisation.

The aim of the present study was to investigate whether there would be task-dependent modulation of ipsilateral M1 representations using an advanced methodological approach with MR navigated TMS. We chose three conditions comparable to Tazoe et al., to determine if unilateral, bilateral homologous and bilateral heterologous/antagonistic contexts would reveal differential iMEP CoG and excitability, hypothesizing that different tasks would lead to differences in the area or CoG of iMEPs.

2. Methods

2.1. Participants

In total, twenty healthy volunteers (10f, mean 26.1 ± 4.6y) participated in the study. All participants were right handed as determined by Edinburgh Handedness inventory (Oldfield, 1971; mean score 94.3). The sample size of this exploratory study was determined based on the previous studies that used samples of less than twenty participants. None of the participants took any medication or had any neurological or psychiatric disorder. All participants gave written informed consent to the experimental procedures, which were approved by the local ethics committee at the University Medicine of Greifswald (BB139/18).

2.2. Structural MRI

A 3T scanner (Verio, Siemens, Erlangen, Germany) with a 32-channel head coil was used for MR imaging. A high-resolution T1-weighted 3D MPRAGE (voxel size 1×1×1mm; 176 slices; matrix size 256 × 256; TR 1.69 ms; TE 2.52 ms) was generated for TMS-neuronavigation.

2.3. Navigated- TMS

During the TMS experiment participants were seated in a comfortable chair, connected to the EMG and registered for frameless neuronavigation. Electromyographic (EMG) activity was recorded from the left and right biceps brachii using a tendon-belly-montage with surface electrodes (10mm Ag/AgCl) Recorded EMG signals were amplified (CED 1902; Cambridge Electronic Design, United Kingdom), band-pass filtered (20 – 1000 Hz) and sampled at 2 kHz (CED 1401). Data were stored for offline analysis using Signal (V6.0, CED).

TMS was delivered through a Magstim Bistim 200 stimulator (MagStim Company Ltd.) with a monophasic waveform. Neuronavigation was performed with a stereo-tactical infrared optical-tracking Polaris camera (Polaris System, Northern Digital, Waterloo, Ontario, Canada) and BrainSight (BrainSight TMS, Rogue Research Inc.). The individual structural MR scan and participant head were co-registered in the Polaris reference frame using 3D-head reference marker attached to the head, with the tragi, nose tip and nasion used as anatomical landmarks. After registration, the left primary motor cortex was localized by identifying the ‘hand knob’ as an anatomical landmark for the motor hand area (Yousry et al., 1997).

2.4. Experimental setup

The figure-eight coil was held tangentially to the scalp at an angel of 45° to induce current flow in a posterior to anterior direction. TMS was delivered starting at the anatomical landmark of the hand knob. For the motor hotspot, the coil was moved until the site eliciting the largest average MEPs in the resting BB contralateral to the simulation side in 5 of 10 stimuli was located.

Hotspot location was stored and used as the center of a 3 × 3 grid with an in-between distance of 2cm, spanning a grid of 4cm × 4cm in total. The aim of this grid was to create a target area covering CoG locations and to reliably stimulate the targets across the three conditions (Zdunczyk et al., 2013). The grid was created using the Brainsight build-in function and was snapped to the individual reconstructed 3D brain surface. Coordinates of the nine iMEP targets including the cMEP hotspot were stored for further offline analyses.

All of the determined 9 stimulation target points were stimulated in a randomized order with 10 pulses at 100% maximum stimulator output (MSO) each to guarantee reliable recordings (Cavaleri et al., 2017).

The iMEP experiment consisted of three different tasks (see Figure 1):

- unilateral contraction: contraction of the left biceps brachii and relaxation of the right arm
- bilateral homologous contraction: bilateral contraction of both biceps brachii;

- bilateral antagonistic contraction: contraction of the left biceps brachii and extension of the right arm.

Participants were asked to keep their head straight at all times and were encouraged to perform an isometric contraction of 50% maximal voluntary contraction in the biceps brachii ipsilateral to stimulation side. Muscle force was visually controlled using a dynamometer. Within the tasks, participants were given time to rest as needed

2.5. Data processing

iMEP onset was defined as timepoint when poststimulus EMG exceed prestimuls EMG by one standard deviation for at least 5ms (Ziemann et al., 1999). iMEP offset was defined as the time point where the EMG dropped below the mean rectified EMG plus one standard deviation for more than 5ms. iMEP onset and offset were determined by visual inspection using a horizontal line marking the mean of the rectified EMG before the TMS stimulus plus one standard deviation. iMEP area was calculated using the following formula: [area of rectified EMG in iMEP duration / (mean prestimulus EMG*iMEP duration)*100] (Tazoe and Perez, 2014), thus iMEP area expressing the relative size of iMEP compared to the prestimulus EMG. The prestimulus EMG was measured 100ms before the TMS stimulus. Background EMG was kept constant over different conditions.

For each of the nine stimulation sites, mean iMEP areas were calculated and ranked separately resulting in nine mean iMEP areas per task per participant.

Locations of individual iMEP-CoGs were calculated using the nine stimulation locations and respective MEP areas as

$$x_{CoG} = \frac{\sum_i a_i x_i}{\sum_i a_i}$$

where α represents the response area in μV at the 3D location vector x for position i of stimulation grid (Miranda et al., 1997). The CoG represents the mean location of stimulation points weighted for the amplitudes of their respective responses.

Coordinates of individual cMEP and calculated task dependent iMEP CoG were normalized to the Colin 27 MNI-brain (Montreal Neurological Institute, McGill University). Comparisons of individual cMEP and iMEP CoG location were performed with a visual approach using the coordinates superimposed on Colin 27 MNI-brain.

2.6. Statistical analysis

Individual mean iMEP area was calculated for each target point of the grid for each task separately. Levene's test was performed to test for heteroscedasticity.

A linear mixed effects model (LMM) was performed with TASK (unilateral, bilateral homologous, bilateral antagonistic) as fixed effect and subject and background EMG as random effects. Analyses were done

twice, with the maximum mean iMEP area target point per task and the iMEP area at the hotspot of the contralateral BB. Significance was set at $p<0.05$.

3. Results

3.1. Center of Gravity

Centre of Gravity for iMEPs overall conditions revealed an antero-lateral shift from cMEP hotspot (MNI coordinates x=-34.2, y=-37.1, z=63.6) to iMEP CoGs. However, iMEP CoGs (MNI coordinates unilateral -36.5, -23.85, 63.3; bilateral homologous -35.8, -23.7, 64.3; bilateral antagonistic -36.5, -24, 63.85), remained constant across the three conditions (Figure 2).

Both cMEP hotspot and iMEP CoGs were located around the handknob of the precentral gyrus, with the cMEP hotspot more medial and dorsal compared to the iMEP CoGs (Figure 3).

3.2. IMEP measurements

IMEPs in left biceps brachii could be elicited in all participants during all tasks. Levene's test revealed homogeneity of variance. The iMEP area, expressing the relative size of iMEP compared to the prestimulus EMG, were comparable between tasks: LMM revealed no significant effect of TASK on iMEP area, neither at the target points with the maximum area ($F=0.01$, $p=0.93$) nor at the cMEP hotspots ($F=0.68$, $p=0.51$). In detail iMEP area was 346.6 ± 310.8% for unilateral, 310.9 ± 232.7% for bilateral homologous and 264% ± 128.6% for bilateral antagonistic movement at the target points with the maximum area (Figure 4), and 185.1%±49.4% for the unilateral, 180.1%±63.43% for bilateral homologous and 188.4%±59.17% for bilateral antagonistic movement at the hotspot of the contralateral biceps brachii.

At the target points with the maximum area, mean iMEP onset was 19.8±2.5 ms for unilateral, 20.4±3.9 ms for bilateral homologous and 20.8±3.1 ms for bilateral antagonistic movement, and mean iMEP duration was 23.9±15.2 ms for unilateral, 21.3±13.7 ms for bilateral homologous and 25.1±16.6 ms for bilateral antagonistic movement.

4. Discussion

Our results indicate that motor evoked potentials of the ipsilateral biceps brachii were obtained from a more antero-lateral location of M1 compared to the contralateral biceps brachii. This location is not depending on task, as the centers of gravity of unilateral, bilateral homologous or bilateral antagonistic upper limb movement do not differ in between. Additionally, no difference on iMEP area could be obtained between the tasks.

4.1. Location of Centre of Gravity

The difference on map CoG indicates that ipsilateral movement might originate from a different location in M1 than the homologous contralateral muscle. This finding agrees with earlier research reporting a different origin for iMEPs compared to cMEPs, but with partly contradictory results for different muscles so far. An antero-lateral shift was reported for iMEP in FDI (Wassermann et al., 1994; Ziemann et al., 1999), whereas an antero-medial shift was reported for the same target muscle as in our study, the biceps brachii, by Tazoe and Perez (Tazoe and Perez, 2014). For more proximal muscles like the latissimus dorsi and the pectoralis major, no difference (latissimus dorsi) or a more posterior location (pectoralis major) was reported for iMEPs (MacKinnon et al., 2004), suggesting that differential excitability might also vary between the target muscles. Furthermore, Chen et al. demonstrated that contralateral and ipsilateral MEPs in FDI are preferentially elicited with different current directions over the primary motor cortex (Chen et al., 2003), again suggesting a spatial distinct excitability.

Both iMEP CoGs and cMEP hotspots were located within Brodman area (BA) 4, indicative of the corticospinal tract involved in the production of voluntary movement (Chouinard and Paus, 2006; Geyer et al., 1996). The CoG of the cMEPs was located more medio-posterior compared to the more antero-lateral CoGs of the iMEPs.

Adjacent to BA4 in this spatial direction is the dorsal premotor cortex (PMd) (Geyer, 2019; Sigl, 2019). The ipsilateral dorsal premotor cortex is involved in self-paced movements (Huang et al., 2004), and especially imaging studies suggests that the caudal part of the PMd plays an important role in motor-coordination and execution of movements (Genon et al., 2017; Genon et al., 2018; Horenstein et al., 2009). In addition, the PMd is involved in modulating the ipsilateral M1 both in an inhibitory and facilitating manner, probably via cortico-cortical connections (Côté et al., 2017; Groppa et al., 2012). Interestingly, after stroke single-pulse TMS over the PMd may give rise to iMEPs of the ipsilateral (unaffected) FDI (Alagona et al., 2001). Such responses are seldom observed with healthy participants. These iMEPs may therefore result from an up-regulation of ipsilateral descending pathways after injury to the contralateral corticospinal tract.

In sum, our results indicate that the activation of the ipsilateral biceps brachii involves distinct neuron populations within the primary motor area at the border to the ipsilateral dorsal premotor area, which further supports the role of the ipsilateral hemisphere for motor execution (Bundy and Leuthardt, 2019).

4.2. Modulation of iMEP

In our study, the CoG location for iMEP was independent of task modulation. Therefore, we could not confirm our hypothesis that the cortical iMEP representation is task-dependent. In addition, we could not demonstrate a relevant task modulation for iMEP area size. This was somewhat unexpected, as Tazoe and Perez (2014) demonstrated a task dependency for the same upper limb conditions compared to our study. Only a few studies also investigated iMEP task dependency. Another study did not observe differences in iMEP amplitudes in the erector spinae during a unilateral vs. bilateral tonic contraction (Jean-Charles et al., 2017). Bawa et al. (2004) investigated ipsilateral MEPs in proximal and distal muscles during rest, phasic or tonic contraction, and demonstrated that iMEPs in BB were only detectable

during phasic, but not tonic bilateral contraction. Methodological differences between the studies might explain the different results to a certain extent, as we here used MR-navigated TMS in a larger sample with more stimuli (10 stimuli per target with in sum 90 stimuli per condition) with 100%MSO as stimulus intensity. Additionally, TMS as well as functional imaging studies reveal complex interaction between bilateral motor and premotor cortices during unilateral vs. bilateral movements (Stinear and Byblow, 2002; Walsh et al., 2008), and even unilateral movements relies on bilateral networks (Beaule et al., 2012). Our data with iMEP CoGs and areas not depending on the task suggest that at least the cortical excitability is not altered during different tasks. Together with the partly contradictory results about the modulatory influence of interhemispheric inhibition (Jean-Charles et al., 2017; Perez et al., 2014) and neck afferent inputs (Tazoe and Perez, 2014), the need for further studies with different methodological approaches becomes clear.

4.3. Limitations

The present study has limitations. The sample size of 20, although relatively large for an iMEP study, may have been too small to detect task-dependent effects. We were able to demonstrate a presence of iMEPs in each participant, but with large interindividual variance. Further investigations might help to reduce this variance, for example using stimulus intensities adapted to motor thresholds rather than fixed protocols, smaller coils with a more focused area of stimulation and larger group size. There were other methodological limitations. Both the calculation of the individual CoG per task as well as the normalization process for analyzing the data may result in a loss of spatial resolution. Although, the high stimulus intensity might also limit the spatial resolution, they do not alter CoG reliability (Littmann et al., 2013; van de Ruit and Grey, 2016). On balance, our novel MR-navigated approach to obtain iMEPs represents and advance over previous studies to date. Additional methodological approaches may be needed to further enhance our knowledge of the distinct underlying pathways and their modulation during different motor tasks.

5. Conclusion

Our findings support the idea that ipsilateral motor pathways are a distinct part of the motor system and play a role in the execution of bilateral upper limb movements.

Declarations

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NS, SS and MG. The first draft of the manuscript was written by NS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figures

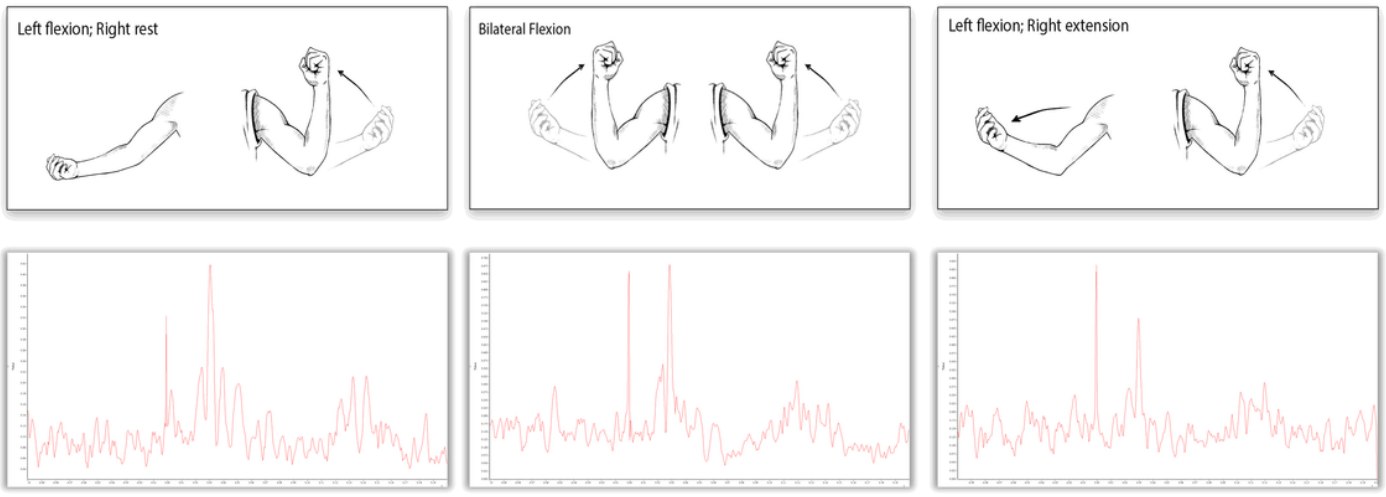

Figure 1

iMEP modulation tasks: a) unilateral voluntary contraction with flexion of the left biceps brachii and relaxation of the right arm, b) bilateral homologous voluntary contraction with bilateral flexion of both biceps brachii, c) bilateral antagonistic voluntary contraction with flexion of the left biceps brachii and extension of the right arm. The lower row shows raw EMG data of a representative subject for each condition.

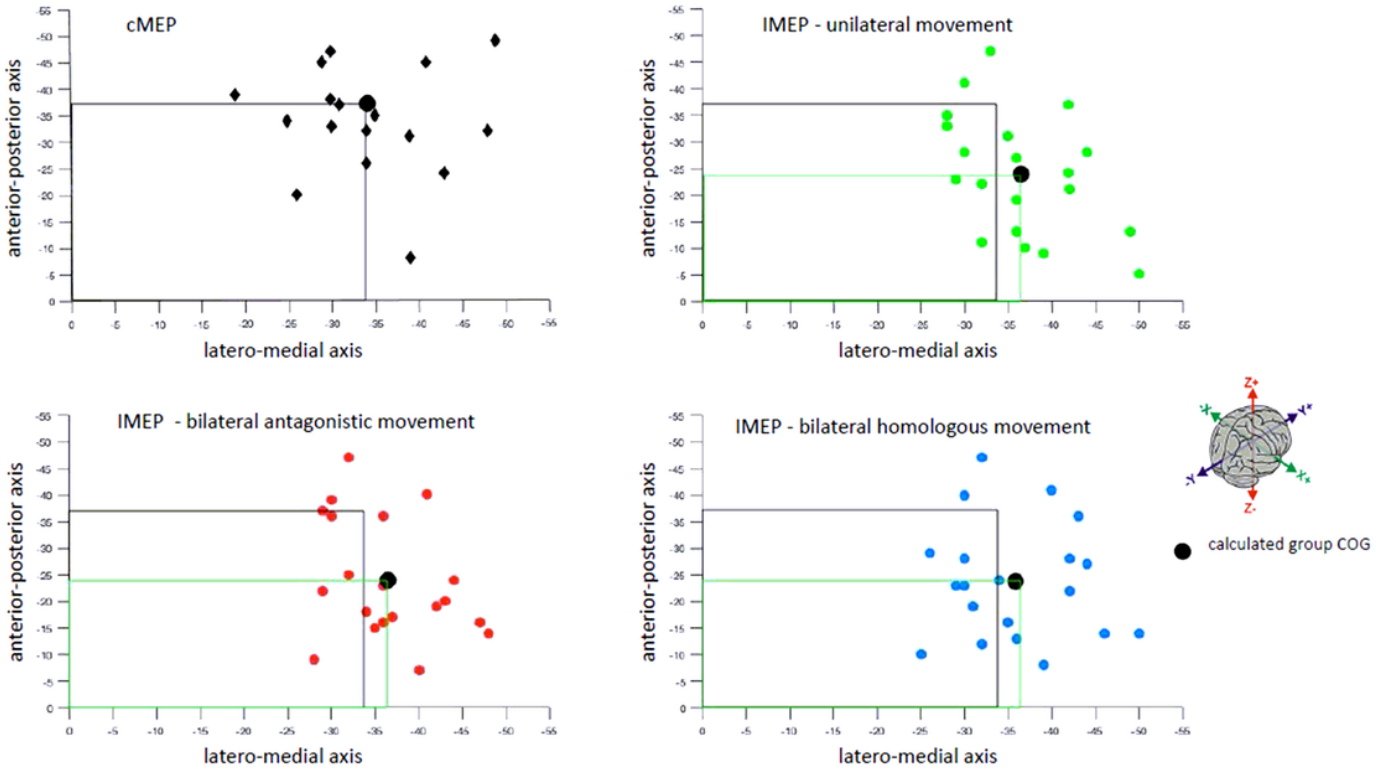

Figure 2

Scatter plot of individual and mean center of gravity (CoG) location for cMEP the three different conditions tested. The black line to the y- and x-axis in all plots shows the cMEP CoG location for comparison.

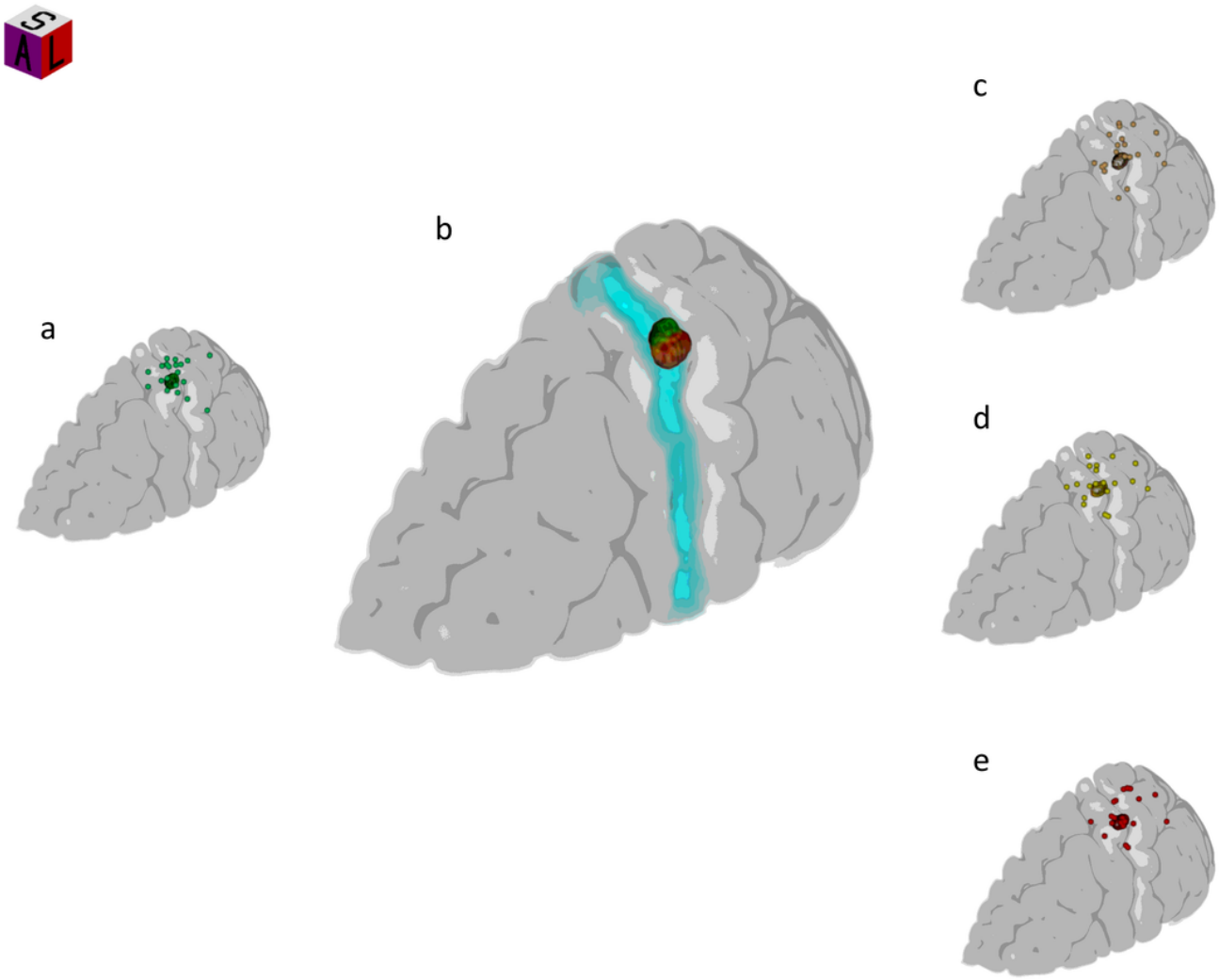

Figure 3

Individual CoG and group mean CoG superimposed on Colins 27 MNI-brain for cMEP (a), and iMEPs during unilateral (c), bilateral homologous (d) and bilateral antagonistic (e) voluntary contraction.

(b) illustrates 95% group mean CoGs (green cMEP, red iMEPs) on Brodman area 4 in turquoise.

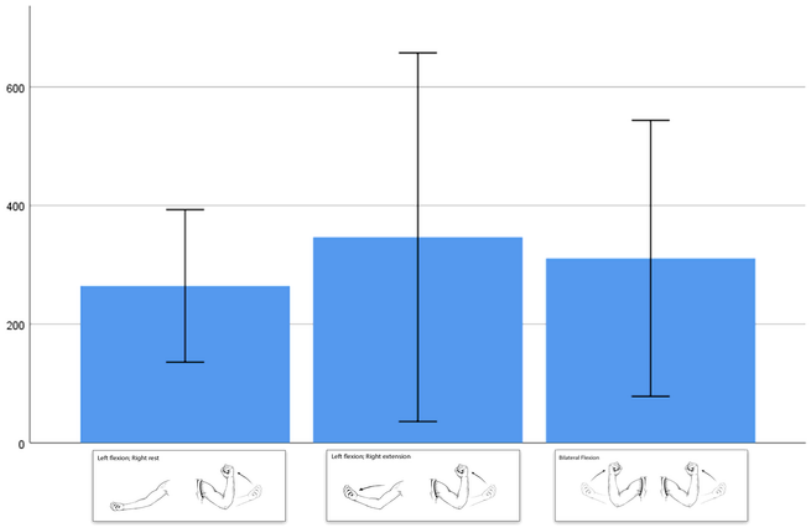

Figure 4

Mean iMEP area (±1SD) in each of the three tasks homologous, unilateral and antagonistic voluntary contraction did not differ.