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Research report

Lateralized asymmetries in distribution of muscular evoked responses: An evidence of specialized motor control over an intrinsic hand muscle

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ABSTRACT

Lateralized neural control over hand muscles has been associated with anatomical and physiological asymmetries in the central nervous system. Some studies suggested that the dominant cerebral hemisphere exhibit larger cortical representation areas with lower excitability, while others reported higher cortical excitability in dominant side compared to the contralateral, or even could not find any differences. Thus, neurophysiological lateral asymmetries are still controversial. This study aimed to evaluate differences in dominant and non-dominant sides in motor evoked potentials (MEPs) distribution and investigate whether conventional montages and high-density surface electromyography (HD-sEMG) provide reliable measurements of corticospinal excitability. MEPs elicited by transcranial magnetic stimulation (TMS) were recorded from dominant and non-dominant sides of healthy right-handed participants with an electrode grid over the *abductor pollicis brevis* muscle. MEPs amplitude distribution, amplitude, latency and resting motor threshold (MT) were evaluated. MEPs distribution significantly shifted towards the lateral direction on the dominant side. MT, amplitude, and latency did not reveal any asymmetries in functional cortical excitability. MEPs amplitude and latency were different for conventional montages and HD-sEMG. Our results suggest that laterality asymmetries manifest in both levels of cortical representation and muscle recruitment, possibly leading to a more pronounced abduction movement on dominant hemisphere compared to the non-dominant side in right-handers. Furthermore, the use of HD-sEMG provided additional insights over conventional electrode montages. A better understanding of laterality asymmetries in fine motor control may help to establish specialized treatments in sensory motor disorders patients.

1. Introduction

The phenomenon of manual laterality or handedness is usually defined as the hand preference to perform unilateral motor tasks. Handedness manifests itself in everyday activities, from merely grasping an object to more sophisticated tasks as handling a musical instrument. Lateralized neural control over hand muscles has been associated with anatomical and physiological asymmetries in the central nervous system. Dominant hemisphere of right-handed subjects may have higher corticospinal tract density (Kertesz and Geschwind, 1971; Nathan et al., 1990). Some authors suggested that the dominant brain hemisphere exhibit larger cortical representation areas with lower excitability (Triggs et al., 1999; Wassermann et al., 1992). In contrast, others reported higher cortical excitability in dominant cerebral hemisphere compared to the contralateral side (Macdonell et al., 1991; Triggs et al., 1994) or even could not find any difference between them (Davidson and Tremblay, 2013; Ferron and Tremblay, 2017; Shibuya et al., 2017; Triggs et al., 1999). Thus, neurophysiological assessment of handedness is still controversial.

Abbreviations: APB, *abductor pollicis brevis*; EMG, electromyography; HD-sEMG, high-density surface electromyography; M1, primary motor cortex; MEPs, motor evoked potentials; MT, motor threshold; TMS, transcranial magnetic stimulation.

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Transcranial magnetic stimulation (TMS) has been used as a valuable tool to study some neurophysiological markers related to laterality. The possibility of non-invasively activate the primary motor cortex (M1) and measure motor evoked potentials (MEPs) provide information about the level of cortical excitability, cortical motor representation area and level of muscle recruitment from both dominant and non-dominant cerebral hemispheres. Even though TMS can be considered as a focal stimulation, it activates a cortical area of about 1 cm^2 and it is more likely to stimulate an underlying neuronal circuitry connected to a group of related muscles rather than evoking the response of one in particular (Classen et al., 1998; Hammond, 2002; van Elswijk et al., 2008). Activation of a group of muscles becomes evident when looking at the spatial distribution of MEPs recorded with high-density surface electromyography (HD-sEMG). Mapping the forearm muscle recruitment by TMS might indicate possible activation of surrounding muscles and provide different spatial distribution of MEPs depending on stimulation intensity (van Elswijk et al., 2008). In this sense, any anatomical or physiological lateral asymmetry underlying the complex neural-motor control may contribute to a possible distinct distribution of myoelectric activity. Moreover, previous studies on handedness recorded MEPs with conventional (~1 cm diameter) surface electromyography (EMG) electrodes in monopolar or bipolar montages. In this case, electrodes detect MEPs over a single, standard position, usually the muscle belly. If there are significant lateral asymmetries or different recruitment of surrounding muscles in dominant and non-dominant sides, using conventional electrodes may provide biased myoelectric responses (Gallina et al., 2017; Souza et al., 2017).

Therefore, this study aimed to evaluate possible asymmetries in muscle-evoked responses spatial distribution related to manual dominance. Additionally, we investigated whether HD-sEMG and conventional monopolar and bipolar montages provide reliable measurements of the cortical motor function while comparing dominant and non-dominant sides. Experimental procedures included the right and left cerebral hemispheres in right-handed subjects in an intrinsic hand muscle, the *abductor pollicis brevis* (APB).

2. Results

Centroids were extracted from the amplitude distribution maps as illustrated in Fig. 1 for a representative subject. There was no significant correlation between the extent of change in centroid coordinates and the laterality index ($r = -0.287$; $P = 0.454$). Additionally, the change in centroid coordinates showed no significant correlation with both amplitude ($r = -0.373$; $P = 0.323$) and latency ($r = 0.180$; $P = 0.644$) differences extracted from the cluster of electrodes. Centroids medial-lateral coordinates differed between each stimulation hemisphere, revealing more lateralized MEPs amplitudes distribution for dominant compared to non-dominant hand ($t = 4.602$; $df = 8$; $P = 0.002$; Fig. 1B). In turn, proximal-distal coordinates were similar for both stimulated cerebral hemispheres ($t = 0.353$; $df = 8$; $P = 0.094$; Fig. 1B), leading to centralized sites of activation in proximal-distal direction in dominant and non-dominant hands.

MEPs amplitude varied across different electrode montages (χ^2 (1) = 6.489; $P = 0.011$) but not for the stimulation side (χ^2 (1) = 0.270; $P = 0.603$). Amplitude was greater for cluster of electrodes compared to the bipolar montage by about 1.55 ± 0.65 mV (mean ± standard error; Fig. 2A). There was also a main effect of electrodes montage (χ^2 (1) = 23.435; $P < 0.001$) on MEPs latency, while no effect of stimulation side was found (χ^2 (1) = 1.231; $P = 0.267$). Latency was greater for conventional bipolar montage compared to the cluster of electrodes by 1.19 ± 0.45 ms (mean ± standard error) and to the conventional monopolar montage by 1.45 ± 0.45 ms (mean ± standard error; Fig. 2B). No statistical difference was identified for interaction between electrode montage and side of stimulation in MEPs amplitude (χ^2 (2) = 0.809; $P = 0.667$)

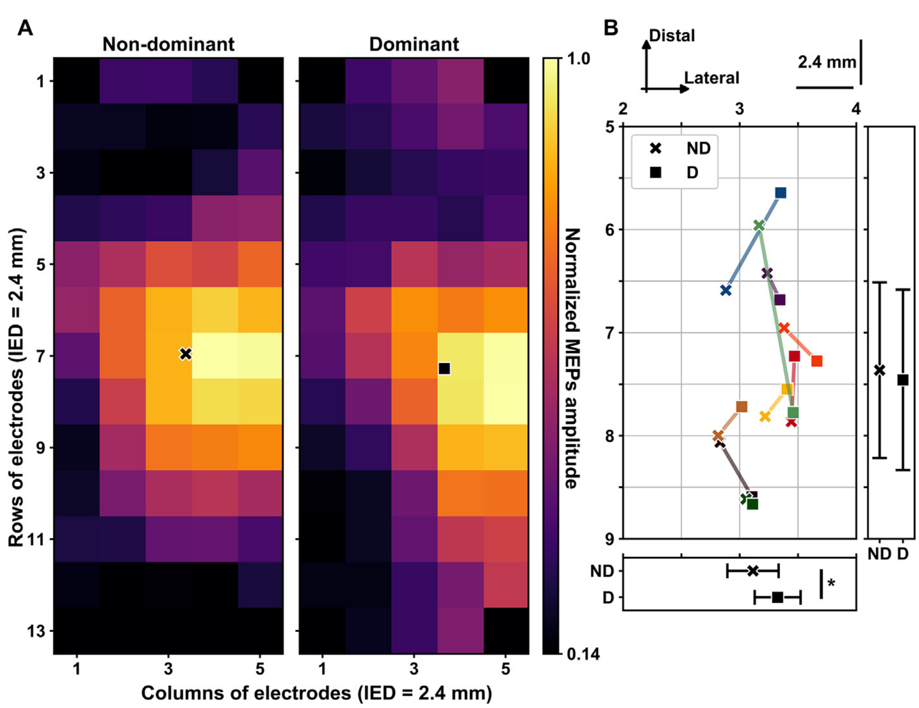

Fig. 1. MEPs amplitude distribution maps and plot of individuals' centroids for dominant (D) and non-dominant (ND) sides. **(A)** Scaled images created with peak-to-peak MEPs amplitude of a representative subject recorded for both sides. Amplitudes were normalized for visualization. **(B)** Centroids of amplitude distribution for each subject in dominant (■) and non-dominant (**X**) sides identified with a unique color and connected by a solid line (n = 9 subjects). Marginal boxplots show mean and standard deviation of coordinates in proximal-distal (right) and lateral-medial directions (inferior; * P = 0.002).

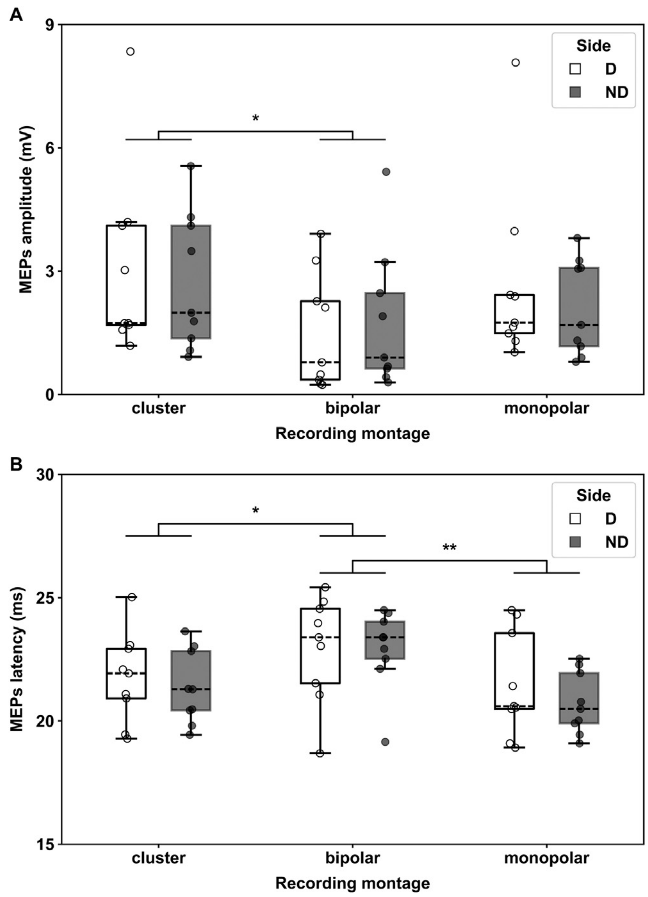

Fig. 2. MEPs amplitude and latency for dominant (D) and non-dominant (ND) sides for each electrode montages, conventional mono- and bipolar montages and grid of electrodes. **(A)** Greater amplitudes were recorded by the cluster of electrodes compared to the bipolar montage. **(B)** Higher latencies were detected by conventional bipolar montage compared to the cluster of electrodes (*P < 0.05 and ***P < 0.001).

and latency (χ^2 (2) = 1.390; P = 0.499). Ultimately, resting MT was similar for dominant and non-dominant hemispheres (t = 0.695; df = 8; P = 0.507), 60 ± 12% and 57 ± 12% of maximum stimulator output, respectively.

3. Discussion

In this study, we investigated possible asymmetries in TMS motor responses associated with hand dominance. Our results showed that MEPs amplitude distributions might differ for the dominant and non-dominant sides. In contrast, resting MT, MEPs amplitude and latency did not depend on the stimulated cerebral hemisphere. Also, we compared conventional surface EMG recording montages to the cluster of electrodes in the grid. Our data revealed higher latencies for conventional bipolar than monopolar montage and cluster of electrodes, and higher MEPs amplitude for the cluster of electrodes compared to the conventional bipolar montage. Clinical and practical implications of our study are discussed below.

3.1. Lateralized asymmetries in MEPs spatial distribution

Analysis of MEPs amplitude distribution revealed a shift in centroid transverse coordinates towards lateral direction for the dominant side compared to the non-dominant side. Moreover, changes in MEPs amplitude distribution seem not to be associated with differences in MEPs amplitude and latency. Centroid in the monopolar amplitude map reflects the distribution of active fibers throughout the muscle and therefore, the location where the highest activity takes place (Farina et al., 2008; Hammond, 2002). Thus, a greater recruitment of muscle fibers within the lateral border of the grid and with amplitude and latency like the contralateral side suggests a more efficient torque generation by the APB muscle in the plane and direction of the thumb abduction movement in the dominant hand. This peripheral differentiation may be complementary to a broader representation of APB muscle in the dominant hemisphere of M1 (Triggs et al., 1999; Wassermann et al., 1992). In fact, a somatotopic cortical organization seems to encode the kinematic aspects of a particular movement rather than recruitment of isolated muscles, and that cortical network may efficiently remodel towards the required motor task (Classen et al., 1998; Rojas-Martínez et al., 2012; Z'Graggen et al., 2009).

Our results suggest that laterality asymmetry manifests itself in both levels of cortical representation and muscle recruitment, possibly leading to a more pronounced abduction movement on dominant hemisphere compared to the non-dominant side in right-handers. The extent of change in centroid coordinates from dominant to non-dominant side did not correlate with the laterality index. In this study, we assessed only nine right-handed volunteers with scores from +50 to +100, which might limit the reach of our physiological interpretations (Triggs et al., 1994). A larger sample with various indexes would possibly provide further insights whether the degree of hand preference affects the shift extent in MEPs amplitude distribution. Furthermore, using a three-axis accelerometer and analysis of motor performance may contribute further to evaluate thumb spatial displacements in both dominant and non-dominant sides.

3.2. Differences between conventional EMG and grid of electrodes

Conventional electrode montages differed from the cluster analysis for both MEPs amplitude and latency. The cluster of electrodes provided higher amplitude than the simulated bipolar recording. One possible reason is that MEPs were extracted from the electrodes with the highest amplitude, which seems to be a more accurate measurement of muscle activation. In this case, selectively recording MEPs amplitude would allow a reduction of TMS stimulus intensity to achieve higher specificity in motor mapping and muscle recruitment (van Elswijk et al., 2008). In addition, a recent study showed that for large muscles, conventional EMG montages might give a biased view due to neighbor muscle activation (Gallina et al., 2017). Therefore, recording MEPs amplitude with HD-sEMG may provide new insights on TMS mechanisms of interaction with the motor system.

Furthermore, the latency from bipolar measurements was higher than from the cluster and monopolar montages. Two different reasons possibly explain these observations. First, spatial filtering in bipolar montage may provide MEPs with later onsets and an increase in latency (Merletti and Parker, 2004). Second, the observed delay might be due to the limited muscle conduction velocity while comparing bipolar to monopolar and cluster montages. The latency of MEPs recorded from the conventional bipolar montage was 1.19 ms and 1.45 ms higher than for those extracted from the cluster of electrodes and the conventional monopolar montage, respectively. Since the electrodes in bipolar configuration were 4.8 mm distant from the center of the grid, the ratio between differences in distance and latency will result in an action potential velocity of about 4 m/s. Corticospinal neurons can generate impulses that reach 70 m/s while a muscle fiber usually reaches between 4 and 5 m/s (Garcia et al., 2004; Merletti and Parker, 2004). Hence, the delay between mono and bipolar protocols might be partially explained by the limited action potential velocity along the muscle fiber and the electrode locations. It is important to notice that MEPs latencies are usually associated with pathologies in corticospinal tract. Thus, comparisons between studies should consider the differences that may arise in MEPs latency and amplitude due to distinct recording techniques (Garcia et al., 2017).

3.3. Laterality and functional cortical excitability

Resting MT, MEPs amplitude and latency showed symmetrical responses for both dominant and non-dominant hemispheres in right-handers. MEPs amplitude reflects the amount of neural drive generated by the TMS pulse in the cortex and latency the delay between cortical action potentials generation and myoelectric activation. On the other hand, resting MT reflects the overall transsynaptic excitability of corticospinal output neurons (Klöppel et al., 2008). Altogether, these parameters have been used to assess the functional activation of motor cortex and their correlation to handedness is still controversial (Hammond, 2002; Shibuya et al., 2017). Our results corroborate several recent studies that reported symmetrical responses of MEPs amplitude, latency, and MT regarding laterality (Civardi et al., 2000; Daligadu et al., 2013; Ferron and Tremblay, 2017; Livingston et al., 2010; Shibuya et al., 2017). Possibly, the organization and circuitry of cortical structures play a more critical role in dexterity of dominant hand rather than the amount of delivered neural drive or conduction time to activate the target muscle. Indeed, it has been shown that motor cortical representation area of intrinsic hand muscles is higher for the dominant compared to non-dominant hemisphere (Volkmann et al., 1998; Wassermann et al., 1992). Moreover, the circuitries of inhibition and facilitation have been pointed out to be stronger and weaker, respectively, for the dominant side (Civardi et al., 2000; Ilic et al., 2004). Also, anatomical studies revealed asymmetries related to handedness, such as more abundant intracortical connections for dominant hand (Amunts et al., 1996). It is important to note that laterality symmetry in MT was observed using a focal figure-of-eight coil over a specific muscle hotspot (Triggs et al., 1999), but not with a large circular coil centered over the scalp vertex (Macdonell et al., 1991; Triggs et al., 1994). In this case, each stimulation methodology seems to activate distinct cortical structures, and thus direct comparison of results has technical limitations.

It has not escaped to our notice that spinal cord may also be a key factor for the lateralized motor behavior. In fact, spinal cord segments in development stage innervating hands show lateral gene expression asymmetries that may modulate behavioral and cognitive processes (Ocklenburg et al., 2017). Possible asymmetries in spinal cord innervating the hand also reinforce our interpretations of a shift in MEPs amplitude distribution towards the lateral direction to promote finer movements in the dominant hand. Ultimately, it has been reported that investigating functional cortical excitability with target muscle under active background contraction might result in motor responses similar to voluntary contractions (Gallina et al., 2017; van Elswijk et al., 2008). It might then be that evaluating motor threshold, MEPs amplitude and latency with background activation is influenced by lateralization in motor recruitment and may reveal different responses for dominant and non-dominant hemispheres.

Patients affected by stroke, Parkinson's disease or lateral amyotrophic sclerosis exhibit disruptions on the motor unit recruitment and discharge patterns (Christakos et al., 2009; de Carvalho, 2012; Hu et al., 2015; Issa et al., 2017). Each clinical condition may affect dominant and non-dominant sides differently (Mitchell et al., 2017). Therefore, laterality asymmetries should be considered when evaluating motor tasks and how they are spatially and temporally adjusted to perform daily skilled activities in which lateral preference matters. Thus, improved knowledge on how the corticospinal excitability and MEPs behave at the level of handedness and under neurological diseases might help to maximize the therapeutic prognostics (Holland et al., 2015).

4. Conclusion

In conclusion, we demonstrated that MEPs amplitude distribution shifts towards the lateral direction in the dominant APB muscle and might suggest a pronounced activation towards the abduction movement. Furthermore, MT, MEPs amplitude and latency assessed at rest did not reveal any lateral asymmetries in functional cortical excitability. Finally, the use of HD-sEMG might provide additional insights over conventional electrode montages for TMS studies. Our study may contribute to further understanding lateral asymmetries of fine motor control and may help to establish specialized treatments for patients affected by sensory motor disorders.

5. Methods and materials

5.1. Participants

Nine volunteers participated in this study (7 men), all right-handed and free from any neuromuscular diseases. Characteristics of volunteers are detailed in Table 1. Handedness was tested with a modified version of the Edinburg Handedness Inventory (Cohen, 2008). Laterality indexes range between −100.0 and +100.0, strong left-handed to strong right-handed, respectively. Only volunteers with laterality index greater than +50 were considered as right-handed (Dragovic, 2004). The study was approved by the ethical committee of the University of São Paulo in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

5.2. EMG recording

MEPs were recorded from the APB muscle with a grid of 61 surface electrodes (13 rows and 5 columns) of 1 mm diameter and inter-electrode distance of 2.4 mm. EMG signals were recorded in monopolar derivation and amplified using an EMG-USB2 system (OT Bioelettronica, Torino, Italy; 12 Bits A/D converter; dynamic range: ±5 V; sampling frequency: 2048 Hz per channel; gain: 500; 2nd order band-pass Butterworth filter: 10–500 Hz). The grid of electrodes was placed over the APB muscle with the midpoint between the scaphoid bone and the base of proximal phalanx of the thumb following SENIAM recommendations (Hermens et al., 2000), as depicted in Fig. 3.

Table 1
Detailed characteristics of all participants. Resting motor threshold of right (MT_R) and left (MT_L) brain hemispheres expressed as % of maximum stimulator output. Laterality index (LI) was obtained with the modified version of the Edinburg Handedness Inventory.

Subject	MT_R(%)	MT_L (%)	LI (index)
1	38	65	100.0
2	49	57	63.0
3	65	72	73.3
4	66	55	96.7
5	55	53	56.7
6	40	45	100.0
7	66	56	100.0
8	72	56	50.0
9	62	85	73.3
Mean ± SD	57.0 ± 12.2	60.4 ± 11.9	68.8 ± 14.7

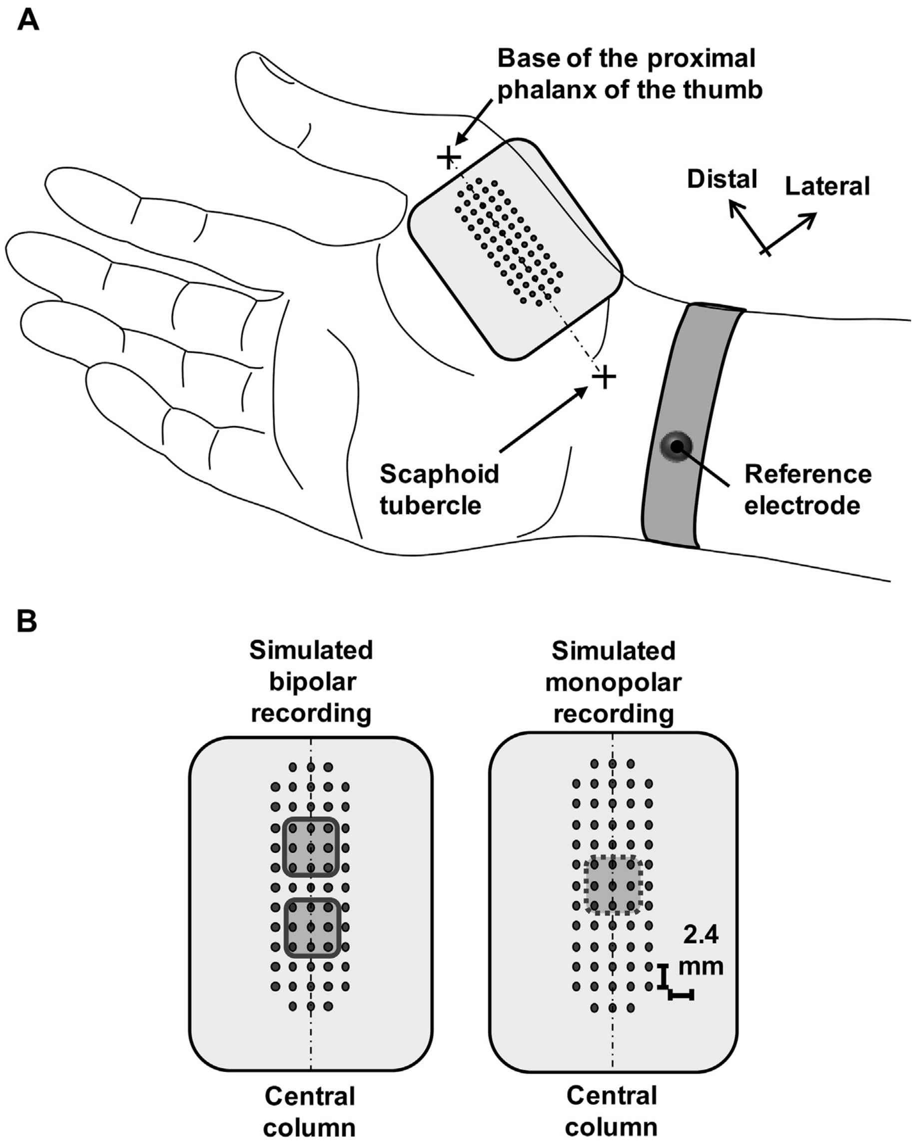

Fig. 3. Schematic representation of EMG recording methods. **(A)** Electrode grid placement over the APB muscle. **(B)** Groups of electrodes in shaded areas were used for simulating the conventional monopolar (left) and bipolar (right) EMG montages.

5.3. Experimental protocol

Participants sat in a comfortable chair and were instructed to stay relaxed with the forearms in prone position throughout the experiment. Visual feedback of the EMG signal was provided to the operators during the entire session to certify that the subject was relaxed. Single-pulse TMS was applied using a figure-of-eight coil connected to a MagPro R30 stimulator (MagVenture, Denmark). Coil center was placed tangentially to the scalp over the APB muscle hotspot and oriented at an angle of 45° about the mid-sagittal line (Bashir et al., 2013; Souza et al., 2017). The APB hotspot was defined as the site over M1 in which a single TMS pulse at a given intensity produced the largest MEPs. Hotspots were marked in a cloth cap with a printed grid of 10×10 mm square. Cap was fixed relative to nasion, inion, left and right ears, cranial anatomic references according to the 10–20 coordinate system of electroencephalography protocols. All subsequent pulses were applied to the marked site. The resting motor threshold (MT) was defined as the minimum stimulation intensity over the hotspot and with relaxed hand muscles, capable of producing MEPs with peak-to-peak amplitude higher than 50 μV in five out of ten trials (Conforto et al., 2004).

To assess the difference between dominant and non-dominant hemispheres on MEPs, ten to thirteen TMS biphasic single pulses were applied with a pseudo-randomized time interval between 5 and 10 s with intensity adjusted to 120% of correspondent MT. The number of pulses was selected to assess each hotspot during approximately one minute and therefore, ensure that coil tilt and orientation were kept constant. Stimulation procedure was performed separately for both left and right cerebral hemispheres with MEPs recordings on the contralateral APB muscle.

5.4. Data processing

MEPs peak-to-peak amplitude and latency were calculated for all electrodes in the grid and each condition of stimulation using the software MEPHunter (Souza et al., 2015) in MATLAB R2013a (MathWorks, USA). MEPs were extracted from the EMG signals detected by each electrode within 45 ms epochs, starting 15 ms after stimulation onset. Signals were visually inspected and where

MEPs were not clearly identified were interpolated with its first eight adjacent neighbors (van Dijk et al., 2009; van Elswijk et al., 2008). An average of four electrodes in each map was interpolated.

Asymmetries in localized muscle response depending on stimulation hemisphere were quantified through the centroid of MEPs amplitude spatial distribution (van Elswijk et al., 2008). Centroid was calculated as the mean coordinate along the medial-lateral direction (columns of the grid), and the proximal-distal direction (rows of the grid) weighted by MEPs amplitude and scaled to maximum grid length in each axis. In addition, the Euclidean distance between the centroid of dominant and non-dominant sides was computed to quantify the extent of change in amplitude spatial distribution for each subject.

Differences in MEPs amplitude and latency between dominant and non-dominant sides were estimated using three detection montages: (i) conventional monopolar recording; (ii) conventional bipolar recording; and (iii) monopolar recording provided by the grid of electrodes. Positioning and size of the conventional monopolar and bipolar recording montages were defined following SENIAM recommendations (Hermens et al., 2000) and signal averaging for simulating conventional electrodes were performed according to previous accounts (Gallina et al., 2017; van Dijk et al., 2009). First, MEPs were extracted from the resulting average of monopolar EMG signals detected by electrodes over the central portion of the grid, between the sixth and eighth rows and the second and fourth columns. Second, MEPs were collected from the difference of monopolar EMG signals detected by two simulated square electrodes with 9.6 mm inter-electrode distance. These arrangements led to detection volumes similar to those monopolar and bipolar recordings typically considered in TMS studies (Corneal et al., 2005), hereafter called simulated conventional monopolar and bipolar recordings, respectively. In this study, each simulated square electrode encompassed a 25 mm^2 area, illustrated in Fig. 3. Finally, a group of electrodes showing the highest MEPs was considered for analysis. In this case, an automated method for segmentation of EMG amplitude maps was applied to identify a cluster of electrodes detecting MEPs amplitudes higher than 70% of grid's maximum (Vieira et al., 2010). Mean MEPs amplitude and latency across segmented electrodes were then calculated for each side of stimulation.

5.5. Statistical analyses

Pearson's correlation was applied separately to evaluate if the extent of change in amplitude spatial distribution is associated to the laterality index, or the MEPs amplitude and latency differences between stimulated sides extracted from the cluster of electrodes. Monotonic relationship and normality of data were checked using scatter and probability plots, respectively. Paired *t*-test was used to compare resting MT from dominant and non-dominant sides. Differences in spatial distribution between stimulated sides were also assessed using paired t-tests for centroid coordinates medial-lateral and proximal-distal. To test whether the electrode montage and stimulated side have effect on the MEPs amplitude and latency, linear mixed model analysis was used with subject as a random factor and stimulated hemisphere (dominant or non-dominant) and electrode montage (cluster grid, conventional monopolar and conventional bipolar) as fixed factors (Bates et al., 2015). Residual plots did not reveal any apparent deviations from homoscedasticity or normality. P-values were obtained by likelihood ratio tests of the full model with and without the effect in question. Post-hoc multiple comparisons were performed using Tukey's test when required. Statistical analysis was performed in R 3.4.0 (R Core Team, Austria) and the level of significance was set at 5%.

Conflicts of interest

none.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.brainres.2018.01.031.

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