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Inter-individual variability in optimal current direction for transcranial magnetic stimulation of the motor cortex

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Abstract

We evaluated inter-individual variability in optimal current direction for biphasic transcranial magnetic stimulation (TMS) of the motor cortex. Motor threshold for first dorsal interosseus was detected visually at eight coil orientations in 45° increments. Each participant ($n = 13$) completed two experimental sessions. One participant with low test–retest correlation (Pearson's $r < 0.5$) was excluded. In four subjects, visual detection of motor threshold was compared to EMG detection; motor thresholds were very similar and highly correlated (0.94–0.99).

Similar with previous studies, stimulation in the majority of participants was most effective when the first current pulse flowed towards postero-lateral in the brain. However, in four participants, the optimal coil orientation deviated from this pattern. A principal component analysis using all eight orientations suggests that in our sample the optimal orientation of current direction was normally distributed around the postero-lateral orientation with a range of 63° (S.D. = 13.70°). Whenever the intensity of stimulation at the target site is calculated as a percentage from the motor threshold, in order to minimize intensity and side-effects it may be worthwhile to check whether rotating the coil 45° from the traditional posterior–lateral orientation decreases motor threshold.

Keywords: Motor cortex; Threshold detection; Current direction; Principal component analysis; Transcranial magnetic stimulation

1. Introduction

The ability of transcranial magnetic stimulation (TMS) to transiently alter regional brain activity makes it a relatively new and powerful addition to the neuroscientist's toolkit. Because the neurophysiology of the TMS effect is incompletely understood, most parameters of stimulation are chosen based on empirical results. In many TMS experiments, regardless of the target site, the intensity of stimulation is calculated as percentage of the motor threshold. The motor threshold is the lowest intensity that reliably activates the intrinsic hand muscles when TMS is applied over the motor strip. Because a muscle twitch is one of the very few directly observable effects of TMS, it is common practice to use the motor threshold as a reference for the cortical excitability. This parameter in turn is highly dependent on the direction of flow of the induced current, which varies with the orientation of the coil (Rosler et al., 1989).

There is consensus that a monophasic current flowing in antero-medial direction in the motor cortex yields the lowest motor threshold (Davey et al., 1994; Mills et al., 1992). During biphasic stimulation the charge accumulation reaches its maximum amplitude during the second pulse (Corthout et al., 2001), and the maximal response is elicited when this second pulse is directed towards antero-medial, with the first pulse flowing postero-lateral (Kammer et al., 2001; Sommer et al., 2006).

Using biphasic stimulation, we have incidentally observed in one of our participants that rotating the coil from the typical orientation to a lateral orientation improved the efficiency of stimulation (motor threshold was 70% of the maximal machine output for an initial current flow in the brain towards postero-lateral and 55% for a lateral current). Previous studies that have measured motor threshold at various coil orientations reported only on the most prevalent optimal current direction but not on the variability of this parameter (Brasil-Neto et al., 1992; Davey et al., 1994; Mills et al., 1992). The aim of the present study was to address the question of inter-individual variability in the optimal current direction for biphasic TMS of the motor cortex. We compared eight different current directions in a sample of ran-

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domly chosen participants in order to estimate the distribution of preferred coil orientations for stimulation of primary motor cortex.

2. Methods

2.1. Participants

Following the identification of a participant in which an atypical orientation was found, we recruited a random sample of 13 healthy, right-handed participants (five female, median age 24, range 21–27). All participants gave written informed consent and the study had approval of the local ethics committee.

2.2. Procedure

Participants were seated upright with their right arm positioned comfortably on a table directly in front of them. Head movements were restrained by use of a chin- and forehead-rest. TMS was performed using a double circular 70 mm coil (maximum output 2.2 T) connected to a biphasic Magstim Rapid stimulator with two external boosters (Magstim Company, Whitland, UK). The site of stimulation was the motor hotspot, defined as the point on the skull where the TMS pulse elicits a maximal evoked motor response in the first dorsal interosseus muscle (FDI) of the right hand. Motor threshold was defined as the lowest intensity that elicited a visible movement in FDI in three out of five stimulation trials.

In order to assess the lowest effective current flow, motor threshold was established by visual inspection for eight different orientations in increments of 45°: anterior, antero-medial, medial, postero-medial, posterior, postero-lateral, lateral and antero-lateral (Fig. 1), similar to the studies by Davey et al. (1994) and Brasil-Neto et al. (1992). To reduce bias in the threshold detection we used a blind design in which one experimenter manipulated the coil, adjusted the intensity of the stimulation and delivered the pulses, and another experimenter who was unaware of the intensity of the stimulation as well as the orientation of the coil inspected the subject's hand to detect whether the TMS pulse triggered a twitch.

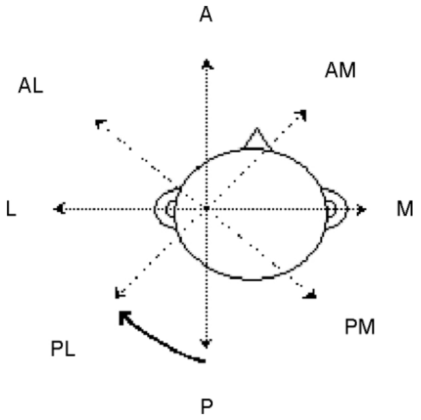

Fig. 1. Conventions for current direction, in increments of 45°. A, anterior; AL, antero-lateral; L, lateral; PL, postero-lateral; P, posterior; PM, postero-medial; M, medial; AM, antero-medial. Principal component analysis angles (Table 1) are related to the AP axis (arrow).

To assess the reliability of the results, each participant did two sessions, performed on separate days, in which all eight directions were tested. Within each session, the order of the directions was randomised.

In the first session, the motor hotspot was located by finding the scalp location that would yield the maximum motor response for an antero-medial induced current. This location would be retained for the second session, by measuring the same distance lateral and anterior from Cz in the 10–20 electrode system. The experiment would then proceed by fixing the coil over this location with a custom coil holder, which allowed for rotational movement only. Participants wore an electrode-cap, on which the locations of Cz and their motor hotspot for the left hemisphere were indicated. An adhesive label (see Fig. 1) which indicated the eight directions was then attached to the cap with the center overlying the motor hotspot, and the posterior–anterior line parallel to the nasion–inion line.

Motor threshold (MT) was then determined for each direction, starting with an intensity of 55% of maximum stimulator output. For each intensity, five pulses would be delivered. If fewer than three out of five trials led to a visible twitch, intensity would be increased in steps of 5%, and this procedure would start again. If three or more out of five trials elicited a response, intensity would be decreased, in steps of 1%, until it was no longer possible to get a positive response in at least three out of five trials. MT was then taken to be 1% higher than this last value.

2.3. EMG recording

In four participants (participants 7, 8, 9 and 11 in Table 1) electromyograms (EMG) were recorded using Ag/AgCl surface electrodes. One electrode was placed on the skin overlying right FDI muscle in the middle of the muscle between the origin and insertion point and the other over a bony prominence on the wrist. The EMG signals were band pass filtered (10–500 Hz), amplified, and sampled at 2000 Hz using a CED1902 signal conditioner and Signal version 3.04 (CED, Cambridge). The EMG-threshold was defined as the lowest stimulation intensity that elicited a motor evoked potential over 50 μV (peak to peak) in 6 out of 10 trials.

3. Results

Test–retest correlation coefficient and the motor thresholds for each current direction are listed in Table 1.

Data from one participant was excluded because the test–retest correlation was under 0.5 (participant 13 in Table 1). In the other 12 participants the test–retest correlation coefficient was between 0.60 and 0.98 with a median of 0.87. In eight participants the lowest threshold for stimulation of the motor cortex was obtained with the first current pulse in the brain flowing in postero-lateral direction (participants 1, 3–9 in Table 1). Data from four of our participants differed from this general pattern, with minimum threshold observed in one of the sessions to cor-

Table 1
Motor thresholds for eight different coil orientations

Subj	Sess	Corr	Motor thresholds at 8 coil orientations								PC angle°
			A	*AL*	*L*	*PL*	*P*	*PM*	*M*	*AM*	
5	1	0.98	70	70	69	**61**	67	70	70	70	38.50
	2		70	70	70	**60**	65	70	70	70	31.27
6	1	0.96	63	69	59	**48**	54	68	61	53	42.76
	2		60	70	59	**49**	55	70	66	55	37.33
4	1	0.95	60	67	54	**46**	53	65	66	58	37.78
	2		60	69	61	**45**	55	70	68	58	34.24
7	1	0.95	67	66	61	**59**	**59**	70	64	60	44.20
	2		69	69	62	**57**	61	78	71	59	47.90
9	1	0.89	66	64	48	**44**	51	63	58	50	36.62
	2		55	66	48	**37**	42	62	55	44	49.76
8	1	0.88	70	88	78	**64**	69	76	80	68	60.18
	2		72	86	74	**59**	68	86	81	62	52.28
2	1	0.86	60	70	57	**48**	56	70	70	56	36.30
	2		59	70	61	54	**47**	69	70	58	24.65
1	1	0.83	65	70	59	**46**	55	70	61	54	45.15
	2		70	64	55	**52**	58	67	66	55	53.56
10	1	0.78	55	66	54	50	**48**	60	58	51	35.63
	2		55	60	53	**48**	**48**	57	58	58	27.35
3	1	0.72	70	70	66	**63**	68	70	70	66	50.18
	2		65	70	65	**64**	70	70	70	65	45.03
12	1	0.70	59	66	50	52	**48**	55	60	60	39.17
	2		62	65	**52**	55	57	67	67	60	42.93
11	1	0.60	**40**	53	53	50	**40**	50	54	51	88.50
	2		50	54	51	**46**	**46**	52	58	50	68.50
13	1	0.41	**24**	29	31	34	**24**	29	30	37	24.95
	2		32	33	36	36	**31**	38	36	33	6.75

Note: Data for each subject is shown for sessions 1 and 2, and subjects are ranked by the between session correlation (Corr). The thresholds are % of machine output, listed by stimulation coil orientation defined by the current direction in the brain for the initial pulse. The minimum threshold for each session is shown in bold, shaded grey. *Abbreviations*: subj, subjects; sess, session; A, anterior; P, posterior; L, lateral; M, medial; AL, antero-lateral; AM, antero-medial; PL, postero-lateral; PM, postero-medial; avg, average; PC angle, principal component analysis estimated optimum stimulus angle (see Fig. 1).

respond to a coil orientation with the first current pulse in the brain towards posterior (participants 2, 10, 12 in Table 1) lateral (participant 12) or anterior (participant 11).

Fig. 2 shows the comparison of motor threshold defined by visual inspection against that of EMG detection. Both measures were highly correlated (Pearson's correlation coefficient, median = 0.98, range 0.94–0.99). On average visual inspection slightly overestimated motor threshold (approx. 2%).

4. Principal component analysis (PCA)

In addition, principal component analysis of the thresholds for all eight tested orientations (using the *princomp* function in Matlab, Mathworks Inc.), estimated the optimal current direction for each participant in both sessions (see Table 1). These estimated angles represent the theoretical optimal angle for that participant, based on the eight uniformly distributed direc-

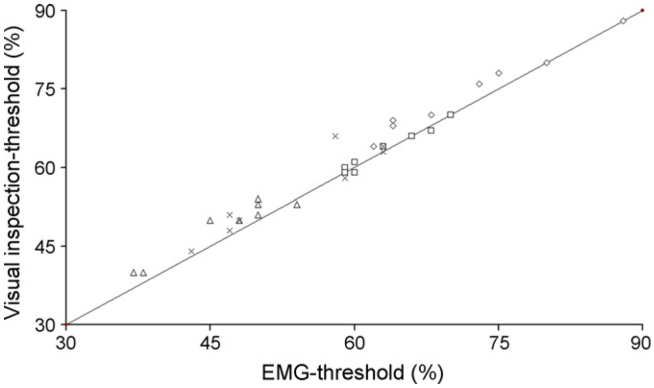

Fig. 2. Correlation between visual inspection-threshold and EMG-thresholds for eight different current directions in four participants—typical participants 7, 8 and 9 (◊, □ and ×) and atypical participant 11 (△). The visual threshold data are listed in Table 1, session 1.

tions that were sampled. PCA angles of the individual sessions ($n = 24$) were normally distributed with the following frequencies: 8.33% between 10° and 20°, 37.5% between 20° and 30°, 29.16% between 30° and 40°, 12.5% between 40° and 50°, 8.33% between 50° and 60°, 0% between 60° and 70° and 4.16% between 70° and 80°. Thus, the estimated optimal angle in our sample varies with a range of 63° (S.D. = 13.70°).

5. Discussion

Motivated by an incidental atypical finding, we estimated the variability of optimal coil orientation for stimulating the motor cortex with biphasic current in a group of randomly chosen participants. In the majority of the participants (8 out of 12) the lowest motor threshold was obtained when the first pulse of the biphasic current flowed towards postero-lateral in the brain relative to the other directions. However, in a third of our randomly chosen participants (4 out of 12) the best current orientation differed from the typical, suggesting that the direction with the most effective induced current varies from brain to brain. An estimate of the optimal angle, using data from all eight directions, suggests that the optimal current direction should be considered as a continuous variable, with the mean around 45° as previously suggested (e.g. Brasil-Neto et al., 1992) but also with a broad intersubject variability (range 63°, S.D. = 13.7°). A previous study with biphasic current that presents the motor threshold in individual participants finds that in all tested participants an initial current pulse in postero-lateral direction is more effective than the reverse orientation (Kammer et al., 2001). That study however evaluated only two directions – antero-medial and postero-lateral – and therefore any deviation of the optimal orientation from this axis would have gone undetected. Our data confirm that in all participants, the postero-lateral orientation for the first current pulse yields a lower motor threshold than the antero-medial. However, we also expose considerable variability and our PCA analysis suggests that the optimal current direction is normally distributed around this axis.

An antero-medial–postero-lateral current which corresponds with the mean of the optimal orientation across subjects in our sample is believed to activate horizontal fibres, which, in the motor cortex, are oriented parallel with this direction (Strick and Preston, 1982). We do not know the reason for the broad distribution of optimal orientation for the lowest stimulus thresholds in our participants. Changing the direction of the induced current affects the shape of the motor evoked potential (Di Lazzaro et al., 2001; Dubach et al., 2004; Takahashi et al., 2005; Trompetto et al., 1999) and the duration of the cortical silent period (Orth and Rothwell, 2004) as if different neural structures or circuits respond optimally at different orientations of the coil. Variations in the microscopic anatomy across subjects may explain this variability of the optimal coil orientation.

The intensity of stimulation has been pointed out to be a critical factor for the optimal current direction, with large intensities (threshold + 20% of stimulator output) being associated with a higher inter-individual variability (Brasil-Neto et al., 1992). To define the motor threshold in this study we have used as a positive response a visible twitch in the intrinsic hand muscles reported by a human observer rather than a motor-evoked potential in an EMG recording as used in the previous studies (Brasil-Neto et al., 1992; Kammer et al., 2001). While there is usually good convergence between motor threshold estimates determined either using the visual method or with the use of EMG (Pridmore et al., 1998), our method may have been less sensitive than EMG detection, leading thus to an overestimated motor threshold and consequently to larger stimulation intensities and an overestimation of inter-individual variability. To rule out this possibility in four of our participants, we repeated the threshold detection procedure using EMG. Visual inspection-thresholds and EMG-thresholds were indeed highly correlated (Fig. 2), and differ by about 2% of stimulator output. This result is also strong validation of the use of careful visual inspection instead of EMG for deciding on stimulation thresholds (Pridmore et al., 1998).

Finally, the validity of many TMS studies relies on the assumption that the induced current is restricted to those sites in the immediate vicinity of the stimulating coil. This assumption is more likely to be met if the stimulation intensity is kept as low as possible. At the same time, lowering the strength of the magnetic field reduces the risk of side effects. Because the coil orientation for minimum motor threshold varies substantially between subjects, our data suggest that it may be worthwhile to check whether rotating the coil 45° from the traditional posterior–lateral orientation decreases the motor threshold.

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