Journal of Neuroscience Methods 328 (2019) 108444

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Short communication

The use of electronic coil location control for focal magnetic stimulation at the cervical level

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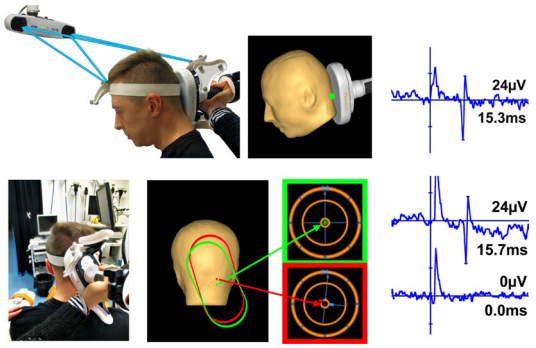
GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Reproducibility
Magnetic stimulation
Motor-evoked potential
Figure-of-eight coil
Cervical spine
Coil location control

ABSTRACT

Background: Accurate re-positioning of the coil is challenging in magnetic stimulation at the cervical spinal level. The applicability of coil location control for this type of stimulation is unexplored.
New method: Utilizing a figure-of-eight coil and anatomy-specific models of the magnetic stimulation system, we developed a novel technique that enables probing corticospinal excitability at the cervical spinal level. Magnetic stimulation was performed in 9 healthy subjects at C2-C6 spinal levels using a figure-of-eight coil and a coil tracking system. MEPs were recorded from the abductor digiti minimi muscle. The functioning of the coil tracking system was tested with an estimated electric field maximum (eEFM) above the C1 cervical level (group 1) and below (group 2). Motor-evoked potential (MEP) reproducibility was assessed with intra-class correlation coefficient (ICC).
Results: The use of coil location control in cervical level focal magnetic stimulation enabled the recording of highly reproducible MEPs. Within one co-registration, the ICC 95% confidence interval (CI) in group 1 was 0.89-0.99 and in group 2 was 0.24-0.85.
Comparison with existing methods and conclusions: This method can be used for accurate maintenance and retrieval of the focal coil position at the cervical level with low spatial variability during stimulation. Existing

Abbreviations: AT, appearance threshold; C, cervical vertebra; eEFM, estimated electric field maximum

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https://doi.org/10.1016/j.jneumeth.2019.108444
Received 11 April 2019; Received in revised form 25 September 2019; Accepted 25 September 2019
Available online 28 September 2019

methodologies employ determination of the coil location based on external landmarks, which makes the procedure cumbersome. This technique can optimize existing stimulation protocols and facilitate development of navigated spinal stimulation.

1. Introduction

Reproducibility of responses to focal magnetic stimulation is essential for studies of corticomotoneuronal excitability and plasticity in test-retest designs. In magnetic stimulation at the cervical level, changes of induced electric field caused by dislocations of the coil and consequent shifts of activation site still remain a major challenge (Mills et al., 1993; Tomberg, 1995; Taylor and Gandevia, 2004). Stimulations are currently performed with non-focal and double-cone coils. The determination of the coil location is performed by using external landmarks, which decreases the accuracy of these methods (Rossini et al., 2015). The applicability of coil location control to overcome these challenges has been unexplored. The possibility to accurate reposition (*i.e.* to "anchor") the stimulation coil with a location control

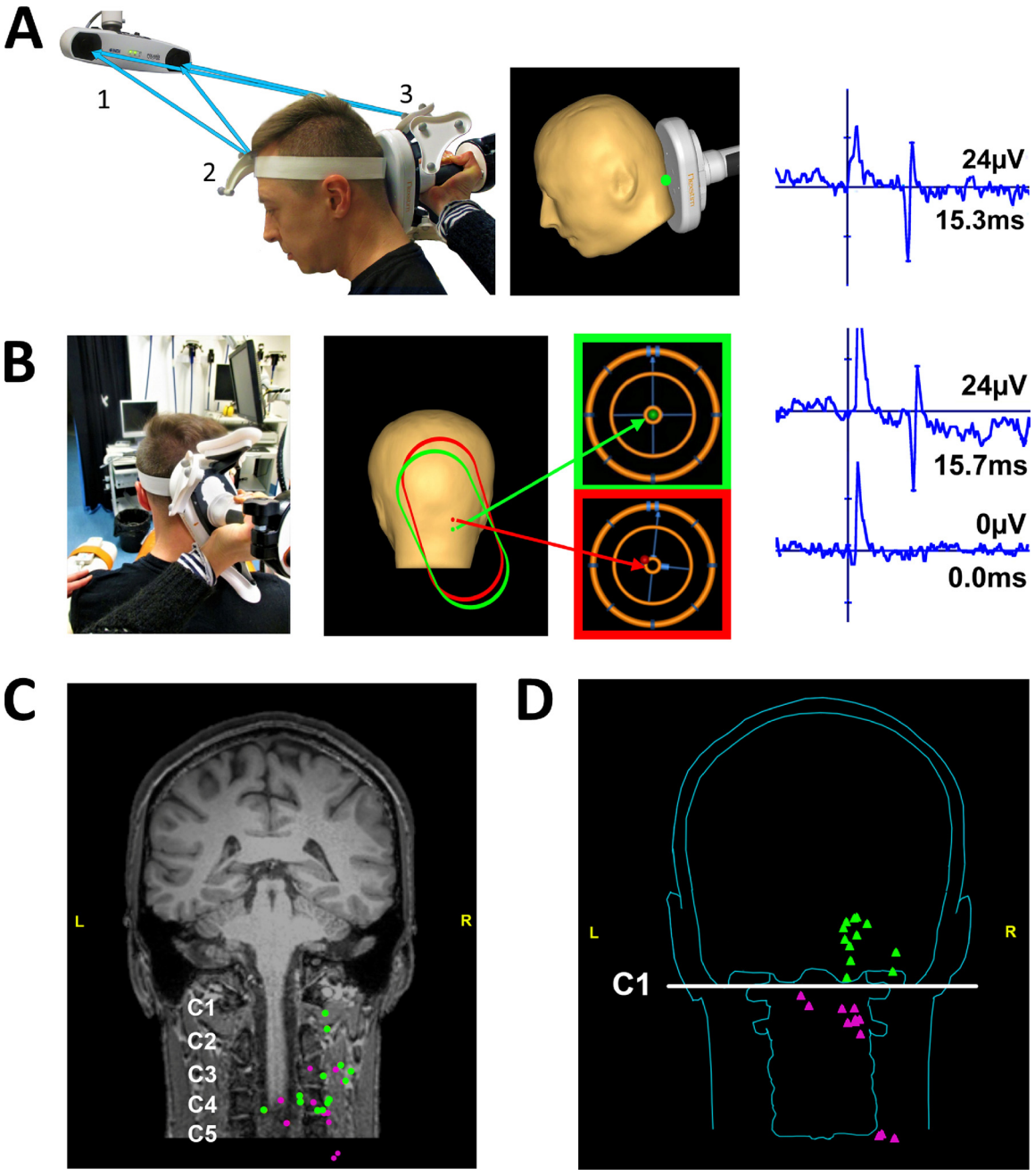


Fig. 1. Location-controlled stimulation. A) Left: position of the tracking unit (1), the head tracker (2) and the stimulation coil (3) for optimal stimulation at the level of the cervical spine. The blue arrows show how the real-time position of the coil with respect to the subject's head is defined. Middle: MRI-based 3-D model of the subject's head (center of the coil is the site where the magnetic stimulus induced a MEP and is marked with a green dot). Right: EMG signal from the NBS software. MEP (amplitude 24 μV; latency 15.3 ms) elicited by the stimulus is visible (note the unipolar stimulus artefact preceding the bipolar response).

system may assist in keeping stimulation parameters constant and enhance measurement reproducibility.

We hypothesized that utilizing the coil location control system, which is based on computing the induced electric field in an individual head 3-D MR image, together with the device for navigated transcranial magnetic stimulation (Ruohonen and Karhu, 2010; Ilmoniemi et al., 1999; Picht et al., 2011), can also be useful in magnetic stimulation at the cervical level.

The neurogeometry at the level of cervical spine is complex and can greatly affect stimulation and measurement accuracy (Mouchawar et al., 1993). The C1 vertebra is attached to the skull. Below the level of C1, movements of the neck in relation to the head, as well as the non-spherical shape of the neck, compromise MRI-head co-registration and the accuracy of electric field computations (Mouchawar et al., 1993). We hypothesized that placing the stimulation coil in a position defined by the estimated electric field maximum (eEFM) on a 3-D head model above the upper border of C1 (but not below) would enable the use of coil location control and result in reproducible motor-evoked potentials (MEPs).

We assessed the reproducibility of MEP amplitudes produced by stimulation at different levels of the cervical spine. We also tested the sensitivity of the location-controlled stimulation by analysing the MEP changes produced by minimal coil dislocations. We also investigated the input-output characteristics of the stimulated sites.

2. Material and methods

2.1. Subjects

Nine healthy right-handed subjects participated in the study (S1-S9, 3 females, mean age ± SD 32 ± 7 years, mean height ± SD 174 ± 4 cm). The study followed safety regulations for magnetic stimulation (Rossini et al., 2015). We asked subjects to report any adverse effects. All subjects provided written informed consent before the experiment. The study was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

2.2. Setup

Biphasic magnetic pulses (length 230 μs, interstimulus interval [ISI] 5 s) were delivered to the neck with the Nexstim eXimia TMS stimulator guided by the eXimia Navigated Brain Stimulation (NBS) system (software version 4.3). The centre of the cooled figure-of-eight coil (outer loop diameter 70 mm) was at the C2-C6 cervical levels. The system could not be used for location control below these levels due to technical restrictions. Spontaneous electromyographic (EMG) activity and MEPs were recorded from the right abductor digiti minimi (ADM) muscle. The ADM muscle is innervated by the ulnar nerve, which originates from the lowermost cervical nerve roots that are the farthest cervical roots from the C2-C6 levels. In addition, the ADM muscle is relatively isolated in comparison with the innervation of other intrinsic hand muscles.

2.3. Stimulation site search

Subjects were in a relaxed semi-sitting position. The head tracker was placed approximately 1–2 cm above the center of the forehead and turned 2–3 cm to the right. The tracking unit was positioned on the right side of the subject. An individual T1 MR image was co-registered to the subject's head (Hannula et al., 2005), which was slightly tilted forward. The coil was placed vertically over the right upper neck with its centre approximately just beneath the palpable lower border of the skull at the C1-C2 level, 2–3 cm from the midline (Fig. 1A). We aimed at eliciting MEPs with the lowest possible intensity as it was expected that at higher intensities the obtained responses are less sensitive to precise coil positioning. The initial stimulation intensity was 50% of maximum stimulator output (MSO). The coil was moved downwards in steps of approximately 1 cm until C5-C6; 1–5 pulses were given at each step. The coil was also turned by 15–30 degrees in both directions to find the position that produced a MEP with amplitude > 10 μV. If no responses were elicited, the stimulation intensity was increased by 5% of the MSO. Three MEP-producing coil positions were found in each subject prior to the experiment; the corresponding coordinates of the eEFM were recorded.

B) Repeating the stimulation. Left: the coil is re-positioned utilizing eEFM to the position of the coil center. The rotation and orientation are identical with those in the upper photo. Middle: the coil position and the center of the coil are superimposed on the head model (green line and dot). Coil position is altered by approximately 15 mm; the new position and corresponding stimulation site are depicted by the red line and dot. Coil positioning is guided by the aiming tool (top image, green frame). The location, tilting and rotation of the coil are indicated by the arrow, bars and the central spot, which lights green when the coil is correctly positioned. Bottom image (red frame) shows the aiming tool when the coil is slightly dislocated. Right: Two corresponding EMG traces represent results of stimulation at the targeted green location and outside it (depicted by red location). Note the similar stimulation artefacts in both responses.

C) Centers of the coil projected on a MR image. Group 1 – green spots, group 2 – pink spots, C1-C5 indicate cervical vertebrae; spatial relations between the centers of the coil and vertebrae in each subject are preserved.

D) eEFMs superimposed on the schematic head. Group 1 – green triangles, group 2 – pink triangles, spatial relations between the eEFMs and C1 cervical level obtained for each subject are preserved.

2.4. Experimental protocol

The experiment was performed on two different days with at least 14 h between measurements. The experiment included three consecutive sessions separated by 20-minute breaks. Each session consisted of stimulation at three previously established coil positions with 5-minute breaks in between (Appendix A2). On the first day, stimulation was performed with the same MRI-head co-registration in three sessions. On the second day, a new co-registration was performed before each session. The appearance threshold (AT) of MEPs was measured for each coil position on the first day by gradually increasing the stimulation intensity with steps of 2% MSO. AT was defined as the intensity at which three consecutive stimuli could elicit a MEP with amplitude ≥10 μV each and stimulation at intensity 1% lower did not elicit any response.

The aiming tool of the TMS device was used for coil re-positioning on the subject's neck, utilizing the eEFM for keeping the coil in the desired position (Fig. 1B). Ten magnetic pulses at 120% of AT (105% for S6) were delivered at each coil position.

2.5. Additional tests: MEP sensitivity to shifts of coil location

To probe the effect of coil position shifts on MEPs, one eEFM-defined position with the highest AT was selected in S3, S4 and S7. Ten stimuli were delivered at each eEFM-defined location. Thereafter, the coil was slightly relocated or rotated in 1–2 mm steps and stimulation was continued until a change in MEP amplitude exceeding 90% of the initial response amplitude was detected. The corresponding coordinates were recorded and 10 stimuli were delivered at the new coil position. Due to low amplitudes, only two coil positions were found in S6.

2.6. Input-output characteristics

We explored the relationship between stimulus intensity and MEP amplitude (input-output characteristics) induced by stimulation. The characteristics obtained at the C7 level of the cervical spine were

compared with the characteristics of neural structures above it in S1 (C2 level), S5 (C4 level) and S6 (C4 level).

The initial stimulation intensity was below AT. It was increased at 3% MSO steps until 90–100% of MSO was reached. Series of three magnetic pulses were delivered at each intensity at random 4–6 s interstimulus intervals. The interval between the series was 20 s. MEPs were recorded from the relaxed right ADM muscle. After a break of several minutes, a similar stimulation was applied at the C7 spinal level without coil tracking (eEFM was not technically possible at this level). The coil was placed over the C7 spinal process. Stimulation was continued up to the intensity of 140% of AT. The data pre-processing was similar to that used for the main experiment. Three amplitude values for each intensity were averaged and plotted for each subject separately in MATLAB.

2.7. Analysis

The data were equally divided into two groups. Group 1 had eEFMs located above C1 in the head model (S1-S3, S5, S6) and group 2 had eEFM below C1 (S3, S4, S7-S9; Fig. 1D). The border between the cerebellum and the occipital lobe in the individual 3-D head model was selected as the upper limit for the eEFMs. Therefore, the data of one eEFM above this level in S1 was omitted. Another eEFM in S4 was excluded from the analysis due to its location on the left side of the cervical spine.

Amplitudes and latencies of the responses obtained in each session were averaged offline for each subject. Mean values for each day and group were calculated by averaging the data of three and six sessions, respectively. The MEP amplitude change between Sessions 1 and 2 was calculated using the formula:

$$S2/S1 = (\text{Amp } S2 \times 100\%)/\text{Amp } S1 - 100\%,$$

where Amp S1 and S2 are mean amplitudes in Session 1 and 2, respectively. The same formula was employed for computation of changes between Sessions 1 and 3. MEP amplitude changes between S2/S1 and S3/S1 were averaged for each day and group separately. Results reported as means ± SD or median and range where appropriate. Reproducibility of MEP amplitudes was assessed using intra-class correlation coefficient (ICC) (Mcgraw and Wong, 1996). ICC was calculated on the basis of two-way analysis of variance (ANOVA) using IBM SPSS for Windows (IBM Corp., Version 24.0.). ICC = 0.5 was used as the theoretical limit of reproducibility. We report absolute agreement of amplitude measurements for each group separately. One outlier in group 1, and 3 outliers in group 2 were excluded from the analysis to make dependent variables normally distributed. Computations were performed with and without outliers. Neither the presence nor absence of the outliers changed the relative position of ICC confidence intervals (CI) with respect to the given threshold. The qualitative description of the results was not affected.

3. Results

MEP amplitudes in group 1 did not significantly differ intraindividually across sessions and between days (Fig. 2A). The median amplitude across 2 days was 23.2 μV (Range R = 371.0 μV) in group 1 and 26.9 μV (R = 374.2 μV) in group 2 (Appendix B). The ICC (3,1) for amplitudes in group 1 across 2 days was 0.73. ICC (3,1) was 0.59 in group 2[1] (see Appendix C for CI). Amplitude ratios of second and third sessions *vs.* first session in group 1 were on average mean ± SD 6.6 ± 6.6% on day 1 (measured within one co-registration) and 19.5 ± 25.8% on day 2 (with new co-registration for each session). The corresponding values in group 2 were 44.0 ± 52.7 and 40.1 ± 32.6% (Fig. 2B). Within one co-registration (day 1), the ICC 95% CI in group 1 was 0.89-0.99 and in group 2 was 0.24-0.85. Thus, placing the eEFM higher than C1 enabled registration of reproducible responses. The amplitude variability was lower and persistence was higher on day 1 with all measurements done within one co-registration (Fig. 2B, Appendix B). The mean latency across 2 days was 15.4 ± 0.1 ms in group 1 and 16.4 ± 0.1 ms in group 2 (Appendix B). The center of the coil was located between C2 and C6 (Fig. 1C) and eEFM above and below C1 (Fig. 1D). The mean AT was 52 ± 11% of MSO in group 1 and 47 ± 6% in group 2.

Both the coil shift and rotation produced abrupt and substantial alteration of MEP amplitudes (increase, decrease or total disappearance). The minimum difference of the coil center coordinates that caused such response changes was 7.1 ± 9.5 mm; the produced changes in the responses before and after coil position shift exceeded three standard deviations (Appendix D).

At the C7 level, where the spinal roots innervating ADM are located, the MEP amplitudes increased steeply with increasing intensity (Appendix E). At the C2-C4 targets in S5 and S6, the amplitude did not initially increase with increasing intensity. After a threshold, a subsequent steep amplitude increase resembling the increase at C7 was observed (Appendix E). In S1, this threshold was not obtained even at 100% of MSO.

No adverse effects were reported. All subjects were responsive to the stimulation.

4. Discussion

We demonstrated that it is possible to use electronic coil location control and obtain reproducible measurements with cervical level magnetic stimulation, although the eEFM does not give information of the electric field in the spinal cord. Earlier studies employed manual coil fixation (Martin et al., 2009; Kobayashi et al., 1995). To our knowledge, this is the first application of the coil tracking system and an MRI-based model for coil re-positioning over the neck. “Anchoring” the stimulation coil to the sites where the eEFMs were located above C1 in the MRI lead to reproducible and persistent MEPs. It was beneficial to record within one head-MRI co-registration.

In three representative subjects, the input-output characteristics of the stimulated neural structures at higher intensities with focal stimulation applied at C2-C4 were consistent with the characteristics of spinal root activation at C7. In addition, the low-intensity part of the input-output curves of C2-C4 suggest that there might be a second activation site with distinct characteristics. The biphasic stimulation employed in the present study is stronger than the monophasic stimulation (Kammer et al., 2001) applied in most previous studies (Mills et al., 1993; Tomberg, 1995; Taylor and Gandevia, 2004), (Martin et al., 2009; Shirota et al., 2011). The mean onset latencies of the MEPs in group 1 were approximately midway between the corresponding values obtained after stimulation of the brainstem (Taylor and Gandevia, 2004; Martin et al., 2009; Shirota et al., 2011) and the spinal roots (Tomberg, 1995; Epstein et al., 1991). The spinal neurogeometry has a strong effect on the induced EF (Mouchawar et al., 1993) and the exact locations of activation sites remain open. Spinal stimulation can potentially activate multiple motor roots and nerves. Moreover, there is still no agreement whether axons of cortical motor neurons descending within lateral motor tracts can be activated by focal magnetic stimulation applied over the cervical spine (Tomberg, 1995; Taylor and Gandevia, 2004; Rossini et al., 2015). In the present study, we recorded motor responses from ADM muscle. The motor roots of ADM are located at C8-T1; we applied the stimulation at the C2-C6 level to study the characteristics of both local activation at smaller intensities and distal activation at higher intensities (Appendix E). This stimulation at lower intensities induced MEPs with latencies different from those previously recorded after brainstem or spinal root stimulation. To clarify the origin of the responses, in addition to coil location control the stimulation

[1] The results are reported without outliers. With outliers ICC (3,1) = 0.99 in group 1 and ICC (3,1) = 0.17 in group 2 correspondingly.

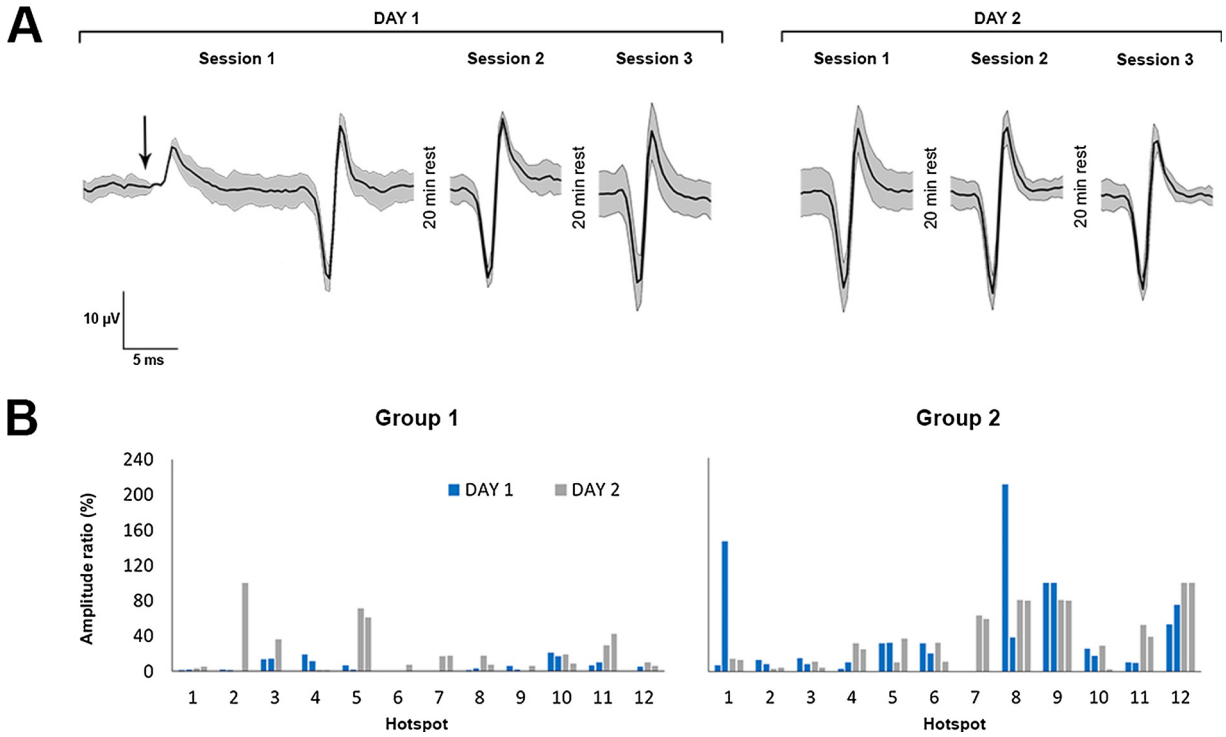


Fig. 2. A) Reproducible MEPs in a representative subject (S1). Ten MEPs were averaged from right ADM at 120% of AT during separate sessions. Grey areas depict 95% confidence intervals. The black arrow indicates the stimulus onset. A unipolar stimulation artefact precedes the actual response for session 1; it is clipped off from responses of subsequent sessions. B) Amplitude ratios calculated individually for each of 12 eEFM-defined coil positions, expressed as the percentage of average MEP amplitudes obtained in second and third sessions *vs.* first session. Blue bars; ratios on the first day, grey bars; ratios on the second day. A low bar indicates good reproducibility.

coils and electric field models suitable for spinal stimulation are needed.

A limitation of the method is that the functionality of the coil location control of NBS system cannot be employed at the C7-C8 levels due to technical restrictions. MR images utilized in the system usually depict cervical spine anatomy up to the C3-C6 level. An attempt to use MRI including the C7 level led to distortion of the corresponding 3-D model and loss of utility due to partial appearance of the shoulders.

Coil location control can be used for reproducible measurements of MEPs with focal magnetic stimulation at the cervical level. The combination of coil location control with the round coil appears to be challenging, if not mutually exclusive, primarily due to a large induced EF that causes spread of activation to several neural sites and decreasing selectivity of stimulation. The proposed new method assists in controlling the variability of MEPs and keeping constant the characteristics of the focal induced electric field and, consequently, the site of excitation. This may be potentially advantageous in contrast to other measurements of spinal excitability such as F-waves, which provide information on only a random fraction of the motoneuron pool (Rossini et al., 2015). The location-controlled magnetic stimulation may be more useful in studies of specific corticospinal pathways.

Acknowledgements

We thank Professor Risto Ilmoniemi for the comments on an earlier version of the manuscript. This work was supported by the Instrumentarium Science Foundation [grant number180031], the University of Helsinki and the Academy of Finland [grant number 307951]. The funding agencies did not participate in study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit it for publication.

Appendix A

Electromyogram recording

Spontaneous electromyographic (EMG) activity and motor-evoked potentials (MEPs) were recorded from the right abductor digiti minimi (ADM) muscle using surface electrodes and eXimia EMG device (sampling rate 3 kHz, band-pass filter 10–500 Hz). A pair of surface self-adhesive electrodes (Ambu Neuroline 720, Denmark) were placed over the muscle belly (active electrode) and the metacarpophalangeal joint of the right little finger (reference). The subject's hand rested on the pillow and the subjects were instructed to keep the upper arm relaxed during the stimulation. Continuous spontaneous EMG activity, including a 200 ms pre-stimulus interval, was visually monitored in real time. Ten magnetic pulses were delivered at each coil position. The total amount of stimuli was increased up to 20–30 pulses in the trials contaminated by muscle activity (35% of trials). After the first day, electrode locations were marked on the skin to enable precise replication of the electrode placement the next day. EMG signals were amplified, filtered, digitized and stored in the NBS computer for offline analysis.

EMG analysis

The 200-ms pre-stimulus and 100-ms post-stimulus intervals were visually inspected. If the pre-stimulus interval was contaminated by

spontaneous muscle activity, the epoch was excluded from the analysis. MEP peak-to-peak amplitudes were manually determined for each epoch. Onset latencies were visually defined from superimposed responses in each series. Responses with an ambiguous onset latency were excluded from the analysis. Persistence was calculated as the number of MEPs out of the total amount of accepted epochs. Responses obtained in 10 consecutive trials were averaged and plotted using a custom-made script written in MATLAB (MathWorks Ltd., USA). The data from two sessions were rejected due to technical error (one session in S3 in group 1 and one session in S8 in group 2). A total of 10% of the epochs in group 1 and 12% of the epochs in group 2 were contaminated by EMG artefacts or were missing due to technical reasons.

Appendix B. MEP characteristics in Group 1 and Group 2

	DAY 1						DAY 2					
	Session 1		Session 2		Session 3		Session 1		Session 2		Session 3	
	Md/M	R/SD	Md/M	R/SD	Md/M	R/SD	Md/M	R/SD	Md/M	R/SD	Md/M	R/SD
Group 1												
Amplitude (μV)	23.9	359.9	25.6	361.4	27.4	360.8	20.2	303.3	22.5	356.7	20.8	371.0
Latency (ms)	15.3	1.4	15.4	1.4	15.5	1.3	15.5	1.3	15.4	1.4	15.5	1.6
Persistence (%)	90.2	14.0	97.3	6.5	92.6	19.0	87.6	27.0	90.6	19.2	82.2	37.4
Group 2												
Amplitude (μV)	24.8	38.7	31.0	59.9	24.7	92.8	44.1	360.3	27.3	107.2	26.3	117.2
Latency (ms)	16.4	1.0	16.4	0.9	16.6	0.8	16.3	0.4	16.4	0.8	16.3	0.6
Persistence (%)	96.4	9.2	90.8	28.7	91.1	28.6	100.0	0.0	84.2	37.0	84.3	35.0

M – mean, Md – median, SD – standard deviation, R – range (R = max-min). M and SD are reported for latency and persistence, Md and R are reported for amplitude. Group 1 included 12 eEFM-defined positions on subjects S1, S2, S3, S5, S6. Group 2 included 12 eEFM-defined positions on subjects S3, S4, S7, S8, S9.

Appendix C. 95% confidence intervals

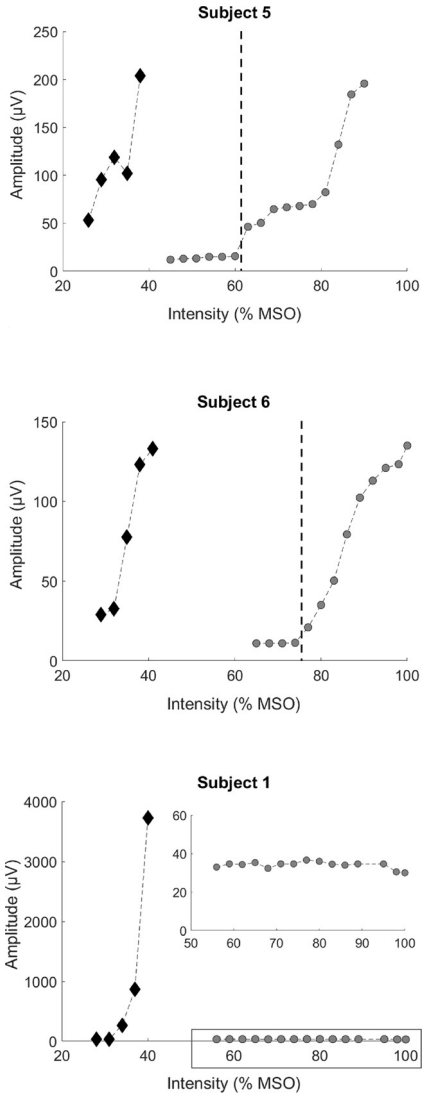
	Group 1	Group 2	Group 1		Group 2	
		Across days	Day 1	Day 2	Day 1	Day 2
Without outliers	0.51–0.91	0.32– 0.86	0.89– 0.99	0.97– 0.99	0,24– 0,85	0,36– 0,91
With outliers	0.99– 0.99	−0.00– 0.50	0.99– 1.00	no outliers	no outliers	0.00– 0.71

Appendix D. Results of the coil relocation test

		Before coil dislocation		After coil dislocation			Coordinates difference		
Sub N	Type of dislocation	Amplitude μV	SD	Amplitude μV	SD	Diff μV	x mm	y mm	z mm
3	Shift	407.5	17.7	0.0	0.0	407.5	0.1	9.0	6.5
3	Rotation	407.5	17.7	15.7	1.3	391.8	0.4	3.2	3.2
4	Shift	29.7	4.6	0.0	0.0	29.7	5.5	5.4	0.3
7	Shift	13.5	0.7	467.8	87.0	−454.3	5.0	5.3	0.4
7	Rotation	13.5	0.7	0.0	0.0	13.5	37.0	18.3	6.3

Diff – difference between mean amplitude values obtained before and after coil dislocation. The coordinate difference was calculated by subtracting coil centre coordinates after coil dislocation from the coil centre coordinates before dislocation.

Appendix E



The relationship between TMS intensity and MEP amplitude in group 1 obtained from S5 (center of the coil located at C4 cervical level), S6 (at C4 level) and S1 (at C2 level). The x-axis depicts stimulus intensity in % of maximum stimulator output, and the y axis depicts the magnitude of MEP amplitudes in μV. Black diamonds; stimulation at the C7-8 cervical levels, grey circles; stimulation at upper cervical levels. Each diamond or circle represents three averaged MEPs at a given stimulus intensity. The dashed line demarcates the plateau and abrupt amplitude growth possibly representing different sites of activation.

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