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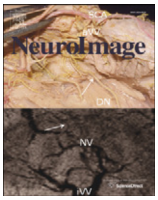

Automated TMS hotspot-hunting using a closed loop threshold-based algorithm

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ABSTRACT

Background: Although neuronavigation is increasingly used for optimizing coil positioning, the inter-session reliability of hotspot location remains unsatisfactory, probably due to the variability of motor evoked potentials (MEPs) and residual investigator bias.
Purpose: To increase the reliability and accuracy of hotspot location we introduce a novel automated hotspot-hunting procedure (AHH).
Methods: AHH is based on resting motor thresholds (RMTs) instead of MEP amplitudes. By combining robotic coil positioning with a closed loop target search algorithm AHH runs independently from the investigator. AHH first identifies all targets with an RMT below a defined intensity of stimulator output (MEP-positive) and then locates the motor hotspot of a target muscle by measuring RMTs at all identified MEP-positive targets. Results were compared to robotic MEP amplitude TMS mapping (MAM) using a 7 × 7 predefined target grid and suprathreshold intensities and manual hotspot search (MHS). Sequence of stimulation was randomized from pulse to pulse in AHH and MAM. Each procedure was tested in 8 subjects.
Results: Inter-session CoG shift was significantly reduced with AHH (1.4 mm (SEM: 0.4)) as compared to MAM (7.0 mm (SEM: 1.8)) ($p = 0.018$) and MHS (9.6 mm (SEM: 2.2)) ($p = 0.007$). No statistical difference was observed between MAM and MHS. RMTs were reliable between sessions.
Conclusion: Our method represents the first fully automated, i.e. investigator-independent, TMS hotspot-hunting procedure. Measuring RMTs instead of MEP amplitudes leads to significantly increased accuracy and reliability of CoG locations. Moreover, by assessing thresholds AHH is the first procedure to fulfill the original hotspot definition.

Introduction

Transcranial magnetic stimulation (TMS) (Barker et al., 1985) is a frequently used tool for the non-invasive investigation of the human motor cortex. Besides its use for the identification of cortical representation areas of muscles, TMS is commonly applied in studies that aim at identifying factors that modulate or influence cortical excitability (Grundey et al., 2012; Lang et al., 2013). For both purposes, the accurate and reliable location of the optimal position for TMS (i.e. motor hotspot) is a substantial part.

However, although studies have recently aimed at improving the reliability of TMS mapping, the inter-session shift of hotspot location is still unsatisfactory ranging from several millimeters (Ngomo et al., 2012) to centimeters (Cincotta et al., 2010; Gugino et al., 2001; Julkunen et al., 2009; Malcolm et al., 2006; Weiss et al., 2013). Since inaccurate coil positioning (Brasil-Neto et al., 1992; Ellaway et al., 1998; Mills et al., 1992; Schmidt et al., 2015), varying distances between the TMS coil and scalp (Richter et al., 2013a), coil rotation and stimulation intensity (Bashir et al., 2013; Di Lazzaro et al., 1998a; Di Lazzaro et al., 2001; Richter et al., 2013a) strongly affect TMS measurements, different neuronavigated systems have been introduced to increase accuracy of positioning (Julkunen et al., 2009; Weiss et al., 2013). However, in addition to the mentioned physical factors, physiological factors, such as voluntary muscle activation (Di Lazzaro et al., 1998b), individual neuroanatomy, differences within the conductivity of brain tissues (Thielscher et al., 2011), time-dependent fluctuations in the subjects' cortical excitability (Lang et al., 2011) and the high variability of motor evoked potentials (MEPs) (Jung et al., 2010; Kiers et al., 1993; Wassermann, 2002).

To overcome the drawbacks of manual TMS mapping and to improve the reliability, we introduce a novel investigator-independent and automated TMS motor hotspot-hunting procedure (AHH). Robotic TMS increases accuracy in positioning (Kantelhardt et al., 2010; Lancaster et al., 2004) and enables automated experiments. Therefore, the influence of the investigator is minimized. To avoid that time-dependent fluctuations in the subjects' cortical excitability bias the results, the stimulation sequence was randomized during the entire experiment. To further reduce the influence of the variability of MEP

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amplitudes on hotspot location we used resting motor thresholds (RMTs) instead of MEP amplitudes as the output parameter. In contrast to MEP amplitudes RMTs remain more stable over time (Lang et al., 2011; Malcolm et al., 2006). Furthermore, AHH is the first TMS procedure introduced to date that fulfills the original hotspot definition, defining the hotspot as the position on the scalp where the threshold is lowest and latency shortest (Rossini et al., 1994). As a feasible procedure for hotspot location has not been available so far (Siebner and Ziemann, 2014) the motor hotspot is usually defined as the position on the scalp where the largest and most consistent MEP amplitudes are evoked with a given stimulation intensity (van de Ruit et al., 2014; Volz et al., 2014).

Materials and methods

Subjects

The study was approved by the ethics committee of the University of Göttingen and complies with the Declaration of Helsinki. Informed written consent was obtained from 11 healthy subjects (3 males) aged 25–40 years (mean: 29 years). All of them were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971).

Experimental setup

For TMS we used a Magstim 200^2 magnetic pulse stimulator and a 70 mm figure-of-eight coil with a peak magnetic field of 2.2 T at the maximum stimulator output intensity (MSO) (Magstim Company, Whitland, UK). For electromyography (EMG) recordings we used surface electrodes (Ag–AgCl) in a belly-tendon montage. The signal was amplified and band-pass filtered from 2 to 2000 Hz (Digitimer D360, Digitimer Ltd.). An A/D converter (CED micro1401 mkII, Cambridge Electronic Design) sampled the signal at 5000 Hz. Software (Signal v4, CED) recorded MEPs on a standard PC.

Prior to the TMS experiments, each subject participated in a magnetic resonance imaging (MRI) scanning session (T1-weighted 3D turbo-fast low-angle shot (FLASH) anatomical image at 1 mm^3 isotropic resolution) to acquire cranial MRI data (3-T Magnetom Trio, Siemens, Erlangen, Germany).

From the MRI data a model of the head surface was created in the robot navigation software (Smartmove, ANT, Enschede, Netherlands). For TMS, a robot (Adept Viper s850, Adept Technology Inc., Livermore, CA, USA) positioned the coil tangentially over the scalp with a rotation angle of 45° in the sagittal plane. With respect to the six degrees of freedom of movement, the positional error of the robot is $\pm$ 0.02 mm. To prevent that inhibitory or facilitatory effects from previous pulses influence the recordings (Kiers et al., 1993) we set the minimum inter-stimulus interval to 5 s. However, the actual inter-stimulus interval varied between 5 and 8 s depending on distance between the stimulated targets due to the movement speed of the robot. Smartmove controlled the movement of the robot for exact coil positioning. Additionally, it is used to register the subjects' head to a reflective marker of an optical tracking system (positional error: $\pm$ 0.5 mm) (Polaris Vicra, NDI Medical, Waterloo, Ontario, Canada) to allow for compensation of head movements. The same software was used for target creation and positioning.

Goal of the study

The goal of the study was to accurately and reliably identify the position on the scalp where the threshold for a target muscle is lowest, i.e. the motor hotspot (Rossini et al., 1994). For this purpose we developed a novel automated and investigator-independent hotspot-hunting procedure (AHH). We further compared AHH to a standard manual hotspot search (MHS) and a robotized standard MEP amplitude based TMS mapping experiment (MAM).

Experimental design

AHH, MAM and MHS were conducted in 8 subjects. 5 subjects participated in all three experiments (2 male), 3 subjects only in the AHH experiment (1 male) and the other 3 only in the MAM and MHS experiments (2 males). The first dorsal interosseus muscle (FDI) was used as the target muscle for all experiments. Experiments were performed with the muscle at rest.

For each procedure two consecutive sessions (one after the other on the same day) were performed. The experimental setup remained unchanged between sessions to exclude interfering factors. The neuronavigation marker and the electrodes remained on the subject and subjects were not allowed to touch or move the neuronavigation marker. Experiments paused every 15 min and there was a break between the sessions. The subjects determined the duration of the breaks and were allowed to move during the breaks. To keep the subjects alert, subjects were allowed to watch documentaries during the experiments.

Automated hotspot-hunting procedure (AHH)

A self-written software script (in Signal v4) controlled the experiment. After the starting parameters were set, AHH ran automatically so that further interaction by the investigator was not necessary. Starting parameters were a predefined grid of potential targets, a starting target in the center of the grid and a given initial maximum stimulation intensity (MSI). The grid of potential targets covered most of the left hemisphere (grid with 7 mm spacing; 17 × 17). It was placed between the vertex and the auricle and was centered in the middle of the medioauricular line. Theoretically, the maximum stimulation intensity is the maximum stimulator output. However, to not extend the time of the experiment and to reduce discomfort we used a lower maximum stimulation intensity. Due to the observation that males generally have higher thresholds than females MSI was set to 50% MSO for males and 45% MSO for females. Thresholds were determined with the maximum likelihood threshold-hunting algorithm (Awiszus, 2003). This probability-based method for the calculation of the estimated threshold consists of delivering TMS pulses with different intensities. Depending on the resulting MEPs ($<$ or $\geq 50\,\mu$V) the algorithm calculates an estimated threshold. The stimulation intensity for the subsequent stimulus is then automatically set to this threshold. This process can be repeated an infinite number of times. The more pulses are applied, the higher the probability that the estimated threshold corresponds to the real threshold. At least 14 stimuli are required for accurate threshold determination(Awiszus, 2011). As a compromise between the time needed and data quality/error AHH ended after a total of 15 stimuli were applied at each target (see below). To further assure a more robust RMT determination within 15 pulses and over the relatively long period of time of the experiment, we added an online outlier control into the algorithm, which automatically controlled if the estimated thresholds converged at each target. If the estimated thresholds at a target were increasing or decreasing monotonically for the last 5 pulses, the preceding MEP (at the respective target) was classified as an outlier. In this case the software automatically discarded the last 6 data points (rollback) (Fig. 1).

Instead of assessing the RMT at one target and then advancing to the next target, the sequence of stimulation was randomized for every pulse during the entire experiment. After each TMS pulse, the robot moved the coil to the next randomly chosen target.

Overall, the entire AHH consisted of three phases (Figs. 2 and 3) with each phase covering a part of the maximum likelihood threshold-hunting measurement. In all phases, targets were picked from a target pool, which was populated or emptied by rules depending on the phase. In the first two phases of the experiment, targets were tested if their threshold was below or above MSI A target was defined as being MEP-positive if TMS at or below MSI evoked an MEP amplitude of $\geq 50\,\mu$V. Targets where two successive stimuli with MSI did not evoke