Original Research

TMS Brain Mapping in Less Than Two Minutes

Mark van de Ruit, Matthijs J.L. Perenboom, Michael J. Grey

Abstract

Background: Transcranial magnetic stimulation (TMS) corticospinal excitability maps are a valuable tool to study plasticity in the corticospinal tract. Traditionally, data acquisition for a single map is time consuming, limiting the method's applicability when excitability changes quickly, such as during motor learning, and in clinical investigations where assessment time is a limiting factor.

Objective: To reduce the time needed to create a reliable map by 1) investigating the minimum inter-stimulus interval (ISI) at which stimuli may be delivered, and 2) investigating the minimum number of stimuli required to create a map.

Method: Frameless stereotaxy was used to monitor coil position as the coil was moved pseudorandomly within a 6 × 6 cm square. Maps were acquired using 1–4 s ISIs in 12 participants. The minimum number of stimuli was determined by randomly extracting data and comparing the resulting map to the original data set. To confirm validity, the pseudorandom walk method was compared against a traditional mapping method.

Results: Reliable maps could be created with 63 stimuli recorded with a 1 s ISI. Maps created acquiring data using the pseudorandom walk method were not significantly different from maps acquired following the traditional method.

Conclusions: To account for inter-participant variability, outliers, coil positioning errors and, most importantly, participant comfort during data acquisition, we recommend creating a map with 80 stimuli following the traditional method.

Introduction

For nearly 30 years, transcranial magnetic stimulation (TMS) has been a valuable tool to study plasticity of the human primary motor cortex (M1), with the first TMS maps being documented in the early 1990s (e.g. [1,2]). Initially, the technique was time consuming and imprecise; however, the development of navigated brain stimulation using frameless stereotaxy [3] improved its repeatability [4,5].

Despite this step forward, the mapping method remains a time consuming technique and its use beyond the research environment remains limited to pre-surgical tumour mapping [6]. The importance of reducing acquisition time is evident from the observation that corticospinal excitability fluctuates with time [7,8] and attention [9,10], and any changes following motor learning are short lasting. Moreover, in clinical practice the time available with a patient is demanding for the patient, thus limiting their use. As a result, numerous studies have reduced acquisition time by compromising the map quality.

Traditionally, data acquisition for a full map requires between 15 and 30 min [11–13], and this can take up to 1 h dependent on the protocol employed [14]. Importantly, this acquisition time does not include preparation time to set up the electromyographic (EMG) recording, determine the most excitable scalp site (commonly referred to as the hotspot) or to determine motor thresholds. Data is typically acquired by stimulating M1 at multiple predefined sites, organized in ~1 cm spaced rows and columns (see Fig. 1A), with...
3–5 stimuli delivered at each site (e.g. [2,15]). Offline, the position data are then matched to motor evoked potentials (MEP) acquired from the EMG data to produce a 2-dimensional contour plot (see Fig. 1C). To reduce acquisition time many investigators now use some combination of shorter interstimulus interval, fewer stimulation sites or fewer stimuli per site.

In the literature, as few as 11 and as many as 225 stimulation sites have been reported [16,17]. Sites are usually distributed in a square or rectangular grid spaced at 1–2 cm (e.g.[18]). Typically, between 3–10 stimuli are administered per site [2,15,19–21] with an interstimulus interval (ISI) set between 3–6 s, although ISI ranges from 1.1–15 s [15,18,22–24]. Acquisition time has been reduced to as little as 2.5–10 min (e.g.[23–25]), although this has been achieved by minimizing the number of stimulation sites (e.g.[25]) or reducing the ISI (e.g.[23,24]). However, the effect of reducing the number of stimuli or ISI on the TMS map has not been validated against the more traditional long mapping protocols. This observation is interesting, as compromising the mapping acquisition parameters has been observed to shift the centre of gravity (COG) of the map, and to change its area and/or volume, with respect to the ‘true’ values [26,27]. This highlights the importance of parameter selection. There is, however, no consensus in the literature about how best to optimize these parameters in order to produce a good-quality map in a short period of time.

Grey et al. [28] used frameless stereotaxy and a pseudorandom walk approach to avoid the problem of accurate coil positioning to predefined targets (see Fig. 1A). When delivering single stimuli in a pseudorandom walk one does not need to repeatedly place the coil in a specific predefined position and orientation, thus ISI may be decreased in order to shorten the acquisition time. No statistically significant difference was observed comparing the grid system (traditional method) and pseudorandom walk method for either of the COG x-y coordinates, suggesting the two methods are comparable. More recently Julkunen [29] confirmed that it is not necessary to use an evenly spaced stimulus grid in order to create a reliable map.

Figure 1. A step-by-step illustration outlining the creation of a TMS map. (A) The traditional mapping method is illustrated on the left and the pseudorandom walk method on the right. The traditional mapping method makes use of a predefined, usually 1-cm spaced grid of target locations, as indicated by the blue markers. Multiple stimuli are successively delivered to each site. In contrast, the new method uses four blue markers to define a boundary without specific targets and within which stimuli are delivered pseudorandomly. The white arrows indicate the direction in which stimuli were acquired. For clarity, these maps are as data are acquired rather than at the end of a trial. (B) A 6 × 6 cm square grid is defined in the neuronavigation software (BrainSight 2.0, Rogue Research) and each stimulation site is matched with the recorded EMG. The motor evoked potential’s peak-to-peak (MEP<sub>pp</sub>) value is extracted in a window between 20 and 50 ms after stimulation. (C) Using a bespoke MATLAB script, a surface is fitted through the 3D position data cloud to create a 2D plane. The 2D position data are then matched with the MEP<sub>pp</sub> data to fit a surface map. This map can be viewed in either a 3D (left) or 2D (right) map. The colour bar represents the MEP<sub>pp</sub> normalized by the maximally evoked electrical response (M<sub>max</sub>). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
By adopting a pseudorandom walk method the stimulation site spacing and number of stimuli per site become redundant parameters. As a result it is only necessary to consider the ISI and the number of stimuli. The aim of this study was to use the pseudorandom walk method to minimize the duration of the data acquisition (excluding preparation and data analysis) required to construct a TMS map. This minimizes the effect of changing attention on corticospinal excitability and allows the method to be more feasible for motor learning and clinical assessments. Therefore, we first determined the minimum ISI at which stimuli could be delivered. Specifically, we examined five ISIs (1, 1.5, 2, 3 and 4 s) and tested the hypothesis that ISIs of 1, 1.5, 2 and 3 s would be different from 4 s \[11,13,18,30–32\], as evidenced by changes in COG, map area and map volume. Second, we determined the minimum number of stimuli needed to create a map, therefore combining the minimum ISI and minimum number of stimuli in order to determine the time needed to create a map. Finally, to ensure validity of the method, we compared maps generated with the pseudorandom walk method to maps generated with the traditional method of data acquisition. This was achieved by comparing COG, map area and map volume between both methods. In addition, we compared within-subject reliability with both methods.

**Methods**

**Participants**

In total, 12 healthy participants were recruited for both experiments in this study (Experiment 1: 24.2 ± 7 y, range 20–46, 5 female; Experiment 2: 23.2 ± 6 y, range 18–35, 8 female), with some participating in both experiments. Participants were screened for contraindications to TMS using a modified version of the TMS adult safety questionnaire \[33\]. The study was approved by the University of Birmingham's Science, Technology, Engineering and Mathematics ethics committee (ERN_12-1189), and all experiments were performed in accordance with the Declaration of Helsinki.

**Electromyography**

Bipolar surface electrodes (Blue Sensor N, Ambu, Denmark) were used to record the electromyographic (EMG) activity of the first dorsal interosseus (FDI). All EMG signals were amplified (500–2 k), band pass filtered (20–1000 Hz), and digitally sampled at 5 kHz to be stored for offline analysis.

**Transcranial magnetic stimulation**

Magnetic stimulation was delivered with a Magstim Rapid² (Magstim Ltd, Dyfed, United Kingdom), using a custom made polyurethane coated 90 mm figure-of-8 coil. The coil was held at 45 to the sagittal plane with the handle pointing in posterior direction to induce biphasic currents in the lateral-posterior to medial-anterior direction, optimal for exciting the area associated with hand and arm muscles \[26,34\]. Stimuli were delivered at a constant participant-specific intensity until the coil position over the scalp was found that evoked the largest MEP (commonly referred to as the hotspot). The hotspot was then marked as a target with the neuronavigation system. With the coil on the hotspot, the resting motor threshold (RMT) was determined according to the definition of Rossini \[35,36\], as the threshold at which 5 out of 10 stimuli evoked an MEP with a peak-to-peak amplitude of 50 μV. In a very few number of cases, this definition could not be used due to noise in the electromyogram that just exceeded 50 μV. In these cases the threshold was determined as the intensity at which at least 5 out of 10 stimuli evoked an MEP clearly discernible from background EMG. Coil position and orientation were monitored throughout the experiment using frameless stereotaxy (BrainSight 2, Rogue Research Inc, Montreal, Canada). To create a map, stimuli were delivered within a rectangular 6 × 6 cm grid superimposed on a generic brain image in the BrainSight 2 software (see Fig. 1A). The grid was placed relative to surface anatomy landmarks (e.g. vertex and ears) in an area that would encompass the hand area of the motor cortex.

**Peripheral nerve stimulation (PNS)**

MEPs were normalized to the electrically evoked maximal M-wave (\(M_{\text{max}}\)) in order to compare across different participants. To obtain the \(M_{\text{max}}\), a bipolar probe was used to stimulate the medial nerve at the level of the elbow using a constant current stimulator (Digitimer DS7A, Digitimer Ltd, Welwyn Garden City, UK).

**Experimental protocol**

The participants were seated comfortably in a chair with the right hand resting pronated on a table. Participants were instructed to keep the hand fully relaxed during the experiments. Online feedback of FDI EMG was provided by displaying a colour, green or red, based on the participant’s root mean square EMG to ensure compliance with this instruction and to focus attention. No direct feedback of the raw EMG was provided to either the experimenter or the participant. One expert TMS experimenter performed all of the testing.

**Experiment 1: Effect of interstimulus interval (ISI) and minimum number of stimuli (N\(\text{stim}\))**

To improve the temporal resolution, this experiment was designed to investigate the effect of ISI and the number of stimuli on centre of gravity (COG), map area and map volume. This experiment was performed with 12 participants. The effect of stimulation frequency was studied using five different ISIs: 1, 1.5, 2, 3 and 4 s. A maximum ISI of 4 s was chosen because an ISI of 3–6 s is commonly reported \[11,13,18,30–32\] and to ensure the experiment would not last longer than 2 h. Each map was created by applying 100 stimuli at 120% RMT in the predefined grid. Stimuli were delivered to random locations within the 6 × 6 cm square. The objective was to ensure two successive stimuli were not delivered in close proximity and that that final map was populated by stimuli with a roughly equal spread across the grid (Fig. 1A). Immediate feedback about stimuli position and orientation were provided by position markers in the neuronavigation display. Three maps were collected for each ISI, with the order of presentation randomized to avoid an ordering effect. To ensure participants would remain focused on their task, a rest period of 1–2 min was given between the maps.

**Experiment 2: Validation to traditional mapping protocol**

This experiment, performed with 12 participants, was designed to validate if a map created using the characteristics found in Experiment 1 would compare to a map using the traditional method. For the traditional method a 6 × 6 cm grid was created from 7 rows and 7 columns with 1 cm spacing. Three stimuli were administered to each site at 120% RMT using a 1.5 s ISI. Maps acquired using the traditional method were compared to maps acquired using the pseudorandom walk method with 80 stimuli at 120% RMT and a 1.5 s ISI as determined in Experiment 1 (see Results Experiment 1). Three maps were collected for each method, with order of presentation randomized to avoid an ordering effect. Similar to Experiment 1, a 1–2 min rest period was provided between maps.
Data analysis

Figure 1 illustrates how the EMG and neuronavigation data were combined to construct a TMS map. Maps were created offline with a bespoke MATLAB script (MATLAB Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States). First, the MEP was quantified by the peak-to-peak value (MEP_{pp}) extracted from a window 20–50 ms after stimulation (Fig. 1B). The corresponding stimulation position was extracted from the neuronavigation data and transposed into a 2D plane. An approximant based surface modelling tool [37], was used to fit a surface through the transposed data. An example of a map in both 3D and 2D are shown in Fig. 1C. A more detailed description of the data processing may be found in the Supplementary Material. Individual stimuli within a map were excluded from analysis if the stimulation or corresponding MEP did not fulfill one of four conditions: 1) the root mean square value of the background EMG (50–5 ms before stimulation) was within Mean ± 2 SD of all stimuli; 2) stimulation at most 10 mm outside the grid border; 3) MEP size not larger than Mean ± 3.5 SD of all MEPs in the map; 4) angle and translation of stimulus within 99% predication interval of all stimuli.

Statistical analysis

Statistical testing was conducted with NCSS 2007 v07.1.4. Tests were considered significant at α = 0.05. As the descriptive statistics showed much of the data violated the standard assumptions of normality (typical positively skewed or uniformly distributed) and equal variance, non-parametric statistics were used for the analysis.

Experiment 1: Effect of interstimulus interval (ISI)

COG was compared between ISIs using the Euclidean distance, hereafter referred to as distance, between each COG and the average COG of ISI = 4 s. An ISI of 4 s was chosen as the benchmark as an ISI between 3 and 6 is most commonly used [11,13,18,30–32]. COG, area and volume were tested using the non-parametric Friedman Test across ISI. Planned post hoc comparisons were performed using the Wilcoxon Signed-Rank Test between ISI = 4 s and all other ISIs. A Bonferroni adjustment was applied to compensate for the multiple comparisons; therefore, in this case α = 0.0125 was used for significance.

Minimum number of stimuli

Post processing to obtain the minimum number of stimuli (N_{sum}) was required to produce a reproducible map. Stimuli were randomly extracted from the map, the map was reconstructed and the correlation coefficient (r^2) was calculated to compare the original and reconstructed map. A map was considered significantly different if either the COG distance exceeded 3.6 mm (75th percentile of COG variability – See Results – Experiment 1) or the r^2 parameter dropped below 0.9.

Experiment 2: Validation to traditional mapping protocol

Mean COG of both the traditional and pseudorandom mapping method was compared using the Wilcoxon Signed-Rank Test. Area and volume were compared using the non-parametric Friedman Test. Post-hoc comparisons were performed using the Wilcoxon Signed-Rank Test. We also examined the reliability of the parameters of the map for both the traditional and the random walk method using the intraclass correlation coefficient (ICC). Measurement reliability was defined according to the ICC, with ICC ≥ 0.75 defined as excellent reliability, ICC between 0.50 and 0.74 as moderate reliability, and ICC ≤ 0.49 as poor reliability [38,39]. The pseudorandom walk method was considered valid when no significant differences for the parameters between the methods were found or, if differences were found, they fell within observed variability. Moreover, the reliability of the COG and map area had to be moderate to excellent (ICC ≥ 0.50). Map volume was not considered in this assessment as findings with respect to reliability are inconclusive [13,21,23,32]. In addition, to classify the between and within-subject variance the quartile coefficient of dispersion (QCD) and standard error of measurement (SEM) was calculated [40]. SEM was calculated for all map parameters as the square root of the mean square error (MSE): SEM = \sqrt{MSE}. The QCD was calculated for map area and volume using: QCD = (Q_{75} - Q_{25})/(Q_{75} + Q_{25}), where Q_{25} and Q_{75} are the 25th and 75th percentile. The centre of gravity measures were excluded from the between subject analysis because we used a generic structural scan for all participants. A between participant analysis of centre of gravity was therefore not valid.

Results

Data exclusion

All participants tolerated the TMS well and completed the study. Individual stimuli were excluded based on background EMG, coil

[Figure 2. Single participant data illustrating TMS maps acquired at three interstimulus intervals (1, 2, and 4 s) using a 6 × 6 cm grid and 100 stimuli at 120% of resting motor threshold. Very similar maps were also acquired at 1.5 and 3 s, but are not shown in the figure to aid clarity. Each black open circle represents the location of a stimulus. Corticospinal excitability is indicated by colour, with blue representing lack of excitability and red representing the greatest excitability. The black cross (×) highlights the centre of gravity. In this participant, neither the centre of gravity, area or volume changed across the five ISIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)]
angle and translation, position relative to the grid and MEP size. In total 8.2% of all stimuli were excluded before analysing the maps (180 maps analysed). Most stimuli were excluded due to either high background EMG (4.2% of the total number of stimuli) or angle and translation of the stimulus with respect to the skull (3.3% of the total number of stimuli). On average, 8.5 (IQR: 7 ± 11) stimuli were excluded per map.

Experiment 1: effect of interstimulus interval (ISI)

In order to study the effect of ISI on the TMS map we compared five different ISIs (1, 1.5, 2, 3 and 4 s). TMS maps collected with 1, 2 and 4 s ISI from a representative participant are shown in Fig. 2. The maps with stimuli delivered at 1 s and 2 s are very similar in shape and activity compared with the 4 s ISI map. In addition, COG is similar in all three maps across all participants, although the

Freidman's test used with the group data revealed a small, but significant difference for COG between the four ISIs (χ²(4) = 17.87, P < 0.01). Post hoc comparisons revealed small differences between ISIs of 1.5, 2 and 3 s compared with 4 s, for the Bonferroni adjusted P-value (0.0125), whilst there was no significant difference between ISIs 1 s and 4 s (Z = 1.56, P = 0.12, Fig. 3A). The COGs of 4 s ISI differed less than 0.7 mm from all other ISIs. Overall, the median Euclidean distance between ISI 1, 1.5, 2 and 3 s compared with 4 s was 2.4 mm (IQR: 1.2–3.6 mm and 10/90th percentiles: 0.7–4.8 mm), with x-direction 1.3 mm (IQR: 0.6–2.3 mm) and in y-direction 1.1 mm (IQR: 0.5–2.5 mm). Neither map area nor map volume revealed significant differences with ISI (area: χ²(4) = 0.47, P = 0.98; volume: χ²(4) = 1.07, P = 0.90) (Fig. 3B and C).

Minimum number

All 180 data sets were analysed in order to calculate the minimum number required to produce a map. In all cases the maps with reduced stimuli were well correlated with the original map with the full complement of data until very close to the minimum cut-off, as determined by a drop in r² or a shift in COG. In 95% of the cases, the minimum number was determined by r² crossing the 0.9 threshold rather than the COG shifting more than 3.6 mm. Figure 4A is a representative example of a set of maps calculated from the same data set.

In this case 6 stimuli were excluded because the background EMG exceeded the activation cut-off, leaving 94 stimuli for the full map. The correlation coefficient dropped below 0.9 after 38 stimuli were randomly removed from the analysis, leaving a minimum number for this data set of 56 stimuli. A map from this data set with 24 stimuli (r² = 0.78) and a different contour is also illustrated. The decrease of r² by extracting stimuli from the map is illustrated in Fig. 4B, dropping below 0.9 at 56 stimuli. Figure 5 shows the minimum number of stimuli calculated across 15 maps for each participant, sorted from participants with the highest to lowest average number of stimuli. This figure highlights the considerable spread in minimum number of stimuli needed to create a map. The median minimum number of stimuli was calculated across all participants as 63 (IQR: 46–74).

Experiment 2: validation to traditional mapping protocol

To validate the pseudorandom technique, a control experiment was conducted to determine if maps collected with this method were comparable to maps acquired in the traditional manner. TMS maps with the two different methods from a representative participant are shown in Fig. 6A. The stimulation sites are marked with black open circles.

It can be observed that the map created using the pseudorandom method is very similar to the map created with the traditional method. No clear difference can be observed in COG and map area of the two methods. Two data sets were omitted from the analysis due excessive ambient noise in EMG recordings; therefore the analysis was performed on 10 participants. The box plots for COG for both x and y directions are shown in Fig. 6B. COG was significantly different between methods in Y (yCOG: Z = 2.48, P = 0.01) but not in X (xCOG: Z = 1.89, P = 0.06). However, the median xCOG and yCOG differed by only 1.2 mm and 2.1 mm, respectively, which falls within the IQR for COG variability observed in Experiment 1. Neither map area nor map volume was significantly different between methods (area: χ²(1) = 0.40, P = 0.53; volume: χ²(1) = 0.16, P = 0.21).

ICCs, SEMs and QCDs for both the traditional and random walk are listed in Table 1. ICCs for xCOG, yCOG and area were moderate to excellent (ICC > 0.74). However, the ICC of the volume for the
A pseudorandom walk method was poor (ICC = 0.63). Whilst small differences in SEM for xCOG and yCOG are observed, 0.7 mm and 0.3 mm, respectively, they are within the variance reported for xCOG and yCOG in Experiment 1. For map area the SEM was 343 for the traditional method and 323 for the pseudorandom method. This difference can be considered negligible with respect to its order of magnitude. For both map area and volume, QCD was smaller for the pseudorandom method (0.2) than the traditional method (0.3–0.4).

**Discussion**

We have demonstrated that it is possible to acquire a TMS map in less than 2 min by reducing the interstimulus interval and by taking advantage of frameless stereotaxy to deliver stimuli in a pseudorandom walk. In addition, we estimated the minimum number of stimuli required to create a TMS map was 63 (IQR: 46–74). To account for inter-participant variability in minimum number of stimuli, and stimuli excluded during data analysis (on average 7–11), we recommend using 80 stimuli. Maps created with the new method are very similar to maps created with the traditional mapping method where stimulation sites are pre-defined. Whilst maps can be created by acquiring data with an interstimulus interval up to 1 s, we recommend using at most 1.5 s to limit participant discomfort. As a result, maps constructed from 80 stimuli acquired with an ISI of 1.5 s can effectively reduce the acquisition time to 2 min.

**How quickly can data be acquired for a TMS map?**

The primary aim of the present study was to improve the acquisition time of the mapping method without reducing the quality of the map. The present study indicates the TMS map can be recorded with an ISI of 1 s. Whilst significant differences in COG were observed between 1.5, 2, 3 and 4 s, they were always very small (<0.7 mm), falling within the overall COG variability of 2.4 mm (IQR: 1.2–3.6 mm). The significant differences reported in this study can therefore be attributed to natural variability as number was taken at 56 when the correlation was 0.9. Removing more stimuli changes the map as shown when only 24 stimuli are left, while the correlation coefficient is still high (0.78). (A) The TMS maps with 94, 56 and 24 stimuli. (B) The correlation coefficient ($r^2$) plotted against the number of stimuli used to create the map. With 56 stimuli, $r^2$ dropped below 0.9.
caused by fluctuating corticospinal excitability. Most importantly, there was no difference in COG between maps acquired with ISIs of 1 s and 4 s. The 2.4 mm COG variability corresponds well to the 3 mm variability in COG reported by others using the traditional mapping method both within and between sessions [25,27,29,41,42]. The present study concentrated on within-session variability. We did not, however, examine between-session variability which has been shown to be larger (6–10 mm) [32,43]. As a result, further testing is warranted to confirm the between session variability of the COG using the pseudorandom walk method.

The observation that the map does not change with shorter ISIs is not surprising. Whilst the use of a 1 s ISI has been associated with lasting depression of excitability of the cortex when administered to a single site repetitively for 4–15 min [44,45], a number of recent observations suggest depression is unlikely to be a problem with the present method. For example, we have recently demonstrated that TMS delivered with an ISI of 1 s for 3 min to the same stimulation site does not change corticospinal excitability [46]. In addition, the use of the random walk method ensures the same site is not repeatedly stimulated and the possibility of reduced synaptic efficiency is further reduced. However, whilst we have demonstrated in the present study that the use of 1 s ISI is technically feasible, stimulating this quickly does have some drawbacks. For example, we have observed that inexperienced users find it difficult to move the coil to a new location with only 1 s ISI. In some cases this leads to increased experimenter error. We noticed some users were not able to maintain the coil orientation correctly on the scalp at the new location because they were focusing on the neuro-navigation software rather than the participant’s head. More importantly, some participants reported discomfort and anxiety when the stimuli where delivered with an ISI of 1 s and had difficulty complying with the instruction to relax the target muscle. For these reasons we advocate using an ISI of at least 1.5 s when mapping with this method, however emphasize that a 1 s ISI does not affect the TMS map if an experienced TMS user performs the mapping and the participant is comfortable with the procedure.

On average the minimum number of stimuli needed to create a reproducible map was 63 (IQR: 46–74). A considerable spread in the minimum number was found between participants (Fig. 5), highlighting the importance of acquiring sufficient data for the TMS map in order to overcome this variability. In post-processing, 7–11 stimuli were excluded from analysis. Therefore, to ensure sufficient data is collected to produce a reproducible map we suggest a minimum of 80 stimuli are required to produce a map with this method. Using an ISI of 1.5 s, a map can therefore be acquired in 2 min. It should be emphasized that this does not include setting up the EMG recording, co-registering the participant’s head to the MRI, finding the hotspot and RMT, and processing of the data to create the map.

### Map variability

The within-session variability of the map parameters can mainly be attributed to MEP variability, although it has been confirmed that maps can be reliably created despite this variability [47]. MEPs are affected by attention [8–10], asynchronous firing of motor units with phase cancellation [48] and a variety of nonphysiological factors such as coil position and coil orientation [49–51]. In this study, we used the commonly adopted 45° coil angle to stimulate the motor cortex which is commonly believed to optimally excite the hand area [36]. Interestingly, it has been suggested that the optimal coil angle should be individually determined [52,53]. However, the benefit is likely to be minor [4]. Whilst individualizing

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**Table 1** Intraclass correlation coefficients (ICCs), standard error of measurement (SEM) and quartile coefficient of dispersion (QCD) for both the traditional and pseudorandom walk mapping method, showing the test-retest reliability and variance of the mapping parameters. Apart for volume, correlation is good to excellent for both methods. This indicates the random walk method is a reliable method for creating TMS maps. The small differences in SEM for both x- and y-coordinate of the centre of gravity (xCOG and yCOG) fall within 1.3 mm and 1.1 mm COG variances reported in Experiment 1. The SEM difference of 20 for map area can be considered negligible with respect to its order of magnitude. QCD is smaller for both map area and volume for the pseudorandom method compared to the traditional method.
the coil orientation might decrease MEP variability it would also increase the mapping time, which is not beneficial for clinical application. In addition the use of electrical field estimates as opposed to RMT has been advocated as a more reliable measure [51,54], however this is not common practice. MEP variability also depends on the muscle studied and the stimulation site, with proximal muscles usually reported to have more variable MEPs than distal muscles and variability increasing as the coil is moved away from the hotspot [26]. Map reliability has also been argued to be sensitive to experimenter error [32,55]. In an attempt to reduce these sources of variability and improve the quality of the map we took several precautions both during data acquisition and in post-processing.

First, to ensure attention was maintained during data acquisition, participants were provided with continuous feedback about the level of EMG which they were instructed to keep between predefined boundaries. In general, participants reported this task as being easy to achieve but also that it required continuous focus to successfully perform. Whereas this task minimized and stabilized background EMG, any trials with increased background EMG were excluded to further minimize MEP variability. Second, the neuro-navigation data was scrutinized offline to ensure coil orientation was consistent throughout the session. Furthermore, the TMS map was made less sensitive to MEP variability by smoothing the data with a Matlab surface fitting tool called ‘gridfit’ [37]. Full details are available in the Supplementary Material. Briefly, local variability in the surface fit was filtered by setting the compliance of the fit with a stiffness setting in the gridfit tool. This setting was determined through extensive pilot testing and maintained constant for all maps analysed in this study. This filtering is especially beneficial in the periphery of the map, where variability in the smaller MEPs has been argued to be source of reduced reliability of the map parameters [21]. As a result, the quality of the map is improved and the number of stimuli needed to construct a map is reduced without compromising information content.

For both the pseudorandom as the traditional method we found the greatest ICCs for xCOG and yCOG. In general most literature supports the notion that COG is a more reliable parameter than either area or volume [13,21,23,32]. We confirmed for the pseudorandom walk method that also area is a reliable measure but this does not hold for volume. The difference in reliability of the map volume between the methods is in line with the equivocal reports earlier [13,21] and is unlikely to be a consequence of the method. Therefore, we recommend focusing on COG and area when analysing TMS maps.

Further considerations

It is interesting to note the increased use of TMS mapping in neurosurgery as a tool for brain tumour localization. This contrasts to its use in studying motor system plasticity and motor rehabilitation, where the technique remains confined to research studies. The present study indicates it may be possible to use a shorter ISI for presurgical mapping, where a 4 s ISI is common practice [6]. However, it must be emphasized that further study in this area is warranted and that the computational method should be validated against existing methods to determine corticomotor representation size [29].

The method to create a TMS map presented here makes it possible to assess cortical organization in less than 2 min. We recommend using at least 80 stimuli to take account for variability. Whilst it is possible to use fewer stimuli and an ISI of 1 s to produce a map in as little as 1 min, maps produced in this manner will be subject to greater error. To tackle the observed variability in the minimum number of data required to produce a map, a potential next step is to develop a system whereby maps are generated online as the data are acquired to provide the researcher direct feedback about the map. Such a method could, for example, use a parameter estimation algorithm (PESI) as has recently been used in this field for threshold tracking [56]. This would negate the need for a minimum number of stimuli as data could be acquired until a robust map is achieved. This would also give the opportunity to improve spatial resolution in areas of interest such as the area in the immediate proximity of the hotspot.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.10.020.

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