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Title: **Locating primary somatosensory cortex in human brain stimulation studies: Systematic review and meta-analytic evidence**

Running head: Locating S1 in human brain stimulation studies

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Abstract

Transcranial magnetic stimulation (TMS) over human primary somatosensory cortex (S1), unlike over primary motor cortex (M1), does not produce an immediate, objective output. Researchers must therefore rely on one or more indirect methods to position the TMS coil over S1. The 'gold standard' method of TMS coil positioning is to use individual functional and structural magnetic resonance imaging (F/SMRI) alongside a stereotactic navigation system. In the absence of these facilities, however, one common method used to locate S1 is to find the scalp location which produces twitches in a hand muscle (e.g., the first dorsal interosseus, M1-FDI), then move the coil posteriorly to target S1. There has been no systematic assessment of whether this commonly-reported method of finding the hand area of S1 is optimal. To do this, we systematically reviewed 124 TMS studies targeting the S1 hand area, and 95 functional magnetic resonance imaging (FMRI) studies involving passive finger and hand stimulation. 96 TMS studies reported the scalp location assumed to correspond to S1-hand, which was on average 1.5 to 2cm posterior to the functionally-defined M1-hand area. Using our own scalp measurements combined with similar data from MRI and TMS studies of M1-hand, we provide the estimated scalp locations targeted in these TMS studies of the S1-hand. We also provide a summary of reported S1 coordinates for passive finger and hand stimulation in FMRI studies. We conclude that S1-hand is more lateral to M1-hand than assumed by the majority of TMS studies.

New and noteworthy

Non-invasive methods of human brain stimulation involve applying electromagnetic stimuli to the scalp. To target a brain area, brain imaging or other measurement methods are used. Here, we systematically review the methods used to target transcranial magnetic stimulation onto the hand area of primary somatosensory cortex. We relate these targeted locations to our own scalp measurements and to a systematic review of functional magnetic resonance imaging data. We find that the most widely-used heuristic to locate the hand area of S1 is not optimal.

Keywords: S1, SI, TMS, TDCS, MRI

1. Introduction

In December 1908, the brain surgeon Harvey Cushing operated on the exposed postcentral gyrus of his patient, a 44 year old man who had recently developed epilepsy. Electrical stimulation to the cortex just posterior to the middle genu (now referred to as the 'hand knob', Yoursy et al. 1997) elicited sensations which the patient, wide awake and fully cooperative, described “*as though someone had touched or stroked the [right index] finger*” (Cushing 1909, p50).

More than a century after these remarkable and pioneering experiments, the localization of somatosensory function in the human cerebral cortex is still under study in neurosurgical patients (Hiremath et al. 2017). In non-clinical experiments with healthy participants, researchers can use non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS, Barker et al. 1985) to study the human primary somatosensory cortex (S1).

S1 covers a large territory along the central sulcus and postcentral gyrus. While ‘S1 proper’ is restricted to BA3b, we consider three distinct somatosensory cortical areas: BA3b, BA1, and BA2 (Geyer et al. 1999), collectively referring to them here as ‘S1’. Within S1 there are several topographically-organized maps of the body, representing the genitalia, feet, and legs medially, the upper arms superiorly, the forearms and hands laterally, and the face and internal organs laterally and ventrally. While the precise location of each body part representation, as well as the gross anatomy and folding of the pre- and postcentral sulci, may vary between people, the overall topography remains remarkably similar to the classic 'homunculus' as drawn by

Penfield and Boldrey (1937; Tamè et al. 2016). The topography in S1 is more finely-grained and more organized than that of neighboring M1 (Hlustik et al. 2001).

This within- and between-person consistency in the locations of different body part representations in S1 allows neuroscientists to aggregate and map the results from different people in studies of cortical somatosensory function. Functional magnetic resonance imaging (FMRI) data can, for example, provide reasonable estimates of the relative locations of body part representations in small samples of healthy participants, even when the data are transformed into the same, standard, coordinate frames (i.e., warping the shape and size of the brain image), and when averaging data over participants (Nelson and Chen, 2008). Likewise, studies using transcranial electrical, magnetic, or direct current stimulation (TES, TMS, TDCS) can rely on the topography of the neighboring primary motor cortex for stimulator placement over the ‘core region’ of a given muscle (e.g., Weiss et al. 2013). Due to this reliable stimulation of the motor areas, along with clear, immediate and objective outputs in the form of stimulation-evoked body movement and muscle activity, good progress has been made in studying the human primary motor cortex in healthy participants (e.g., Raffin et al. 2015).

Progress has been slower, however, in understanding the electrical excitability of primary somatosensory cortex and its function in healthy participants. This is likely due, in part, to the lack of direct, immediate, and objective consequences of S1 stimulation. While some early studies reported that TMS over M1 or S1 elicited 'paraesthesias' or 'sensations of movement' in healthy participants (Amassian et al.

1991; Sugishita and Takayama, 1993), this phenomenon has not received systematic experimental attention (though see, e.g., Ragert et al. 2003; Tegenthoff et al. 2005, for anecdotal and pre-experimental evidence). The lack of immediate objective consequences following TMS over S1 means that researchers cannot be sure that the stimulating coil is correctly positioned, or that the stimulating current is sufficiently strong or properly oriented to activate the targeted neurons in S1. Reliable coil positioning is critical both to ensure stimulation of the correct brain area, but also to ensure adequate control of TMS-related side-effects (Meteyard & Holmes, 2018; Holmes & Meteyard, under review).

In previous work (Tamè & Holmes, 2016), we used individual FMRI neuronavigation to locate S1-hand in 20 healthy participants during a TMS study of tactile detection and discrimination. We noticed that, in every participant, the scalp location of S1-hand (specifically, the index and middle finger representations) was lateral to the scalp location of M1-hand (specifically, the first dorsal interosseus muscle representation, M1-FDI). This surprised us, as almost all the TMS literature that we were aware of had moved the TMS coil posteriorly to M1-FDI rather than laterally. Further, FMRI studies in which both M1 and S1 were measured in the same participants also showed that the S1 representation was lateral to the M1 representation of the hand (Blatow et al. 2011).

The purpose of the present systematic review was therefore to summarize the available evidence concerning the location on the human scalp which researchers stimulate in TMS studies of S1, in particular the S1 representation of the hand and fingers (S1-hand). We did this in several ways. First, we summarized all the available scalp measurements that we have collected during 35 previous TMS experiments conducted in our own laboratory. Specifically, we summarised those data pertaining to head size and the likely scalp coordinates overlying the representation of M1-FDI, which is often used as a reference-point for TMS studies of S1, along with the location of the C3/C4 electrode location in the 10:20 system (Jasper, 1954), another commonly-used reference. The purpose of systematically measuring the scalp in our prior work is to relate our TMS data to the 10:20 system, to measure between-participants variability in head size and shape, to provide informative prior estimates to assist future localizations, and to provide a check for measurement errors that may arise during neuronavigation. Second, we systematically reviewed the methods used to locate human S1-hand in previous TMS studies, focusing on the scalp locations targeted. Third, we reviewed previous attempts to relate positions on the scalp to the underlying positions in the brain. Finally, we systematically reviewed the brain locations activated following passive finger and hand stimulation in FMRI studies. These four components of the present work allowed us to relate the scalp locations stimulated in prior TMS studies of S1-hand, to the likely location of S1-hand in FMRI studies.

Materials and methods

All experimental studies received approval from local research ethics committees, and were conducted in accordance with international safety guidelines (Rossi et al. 2009), and with the Declaration of Helsinki (2008 version, which does not require study pre-registration). Throughout the manuscript, we refer to scalp and brain coordinates using the following convention: ORIGIN(lateral,anterior). For example, 5cm left and 1cm anterior to the vertex origin, Cz, is written: Cz(-5,1), and 2cm posterior to the FDI muscle location is FDI(0,-2). Standard MNI neuroimaging coordinates are given as MNI(X,Y,Z), in mm. MRI data reported in Talairach and Tournoux (1988) coordinates were converted to MNI coordinates using Matthew Brett's tal2mni.m script implemented in several Matlab functions (http://eeg.sourceforge.net/doc_m2html/bioelectromagnetism/mni2tal.html). All data and analysis scripts are available at https://osf.io/c8nhj/.

Head size and 10:20 locations

The Hand Laboratory has been recording scalp locations during TMS experiments since 2012, and more thoroughly and systematically since 2016 (Protocol sheet available at https://osf.io/c8nhj/). Researchers measured the distance between nasion and inion, and between the pre-auricular points of the two ears. The intersection of these lines is marked as the vertex. For sites relatively close to the vertex and/or close to the pre-auricular axis (e.g., M1, S1), a rectangular coordinate frame (x-axis = right of vertex, y-axis = anterior to vertex) is suitable. For areas further away from vertex, this system would break down with the curvature of the skull, and a polar coordinate scheme is required. The lateral coordinate of a scalp location is always measured first, and the anterior coordinate second, measuring perpendicularly forwards or backwards from the vertex-preauricular line. The data are noted first on the protocol sheet, and transferred later to an electronic database (MySQL, accessed via custom web-based software ARM and LabMan, https://github.com/TheHandLab). As these scalp location data accumulate, they will be made freely available via the TMS-SMART website (http://tms-smart.info). The HandLab database was queried for all available head measurements (N=284), aggregated by participant (N=101). Mean and SD within and between participants was calculated. The standard 10:20 system electrode locations C3/C4, often used in transcranial stimulation studies of S1-hand, were converted into distances measured along the scalp from the vertex by dividing the inter-preauricular distance by 5 (i.e. 20%). Note that head size and shape is likely to vary widely across participants, probably more so than brain size and shape (Zilles et al. 2001; Xiao et al. 2018).

TMS over M1-FDI

The HandLab database was queried for the mean scalp location stimulated during our TMS studies of primary motor cortex, specifically the contralateral representation of the FDI (N=127), aggregating the data by participant (N=65) and hemisphere. Measurements from the same participant were averaged prior to averaging across participants.

Systematic review of TMS over S1-index

PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) was searched with the query "(somatotop* OR somatosens* OR tact* OR touch OR cutan*) AND (TMS OR TDCS OR transcranial stimulation)" on 2nd January 2018, and again on 30th July 2018. The primary variables assessed were the methods used to locate the TMS coil over S1, including the body part targeted, anatomical reference points, coordinate system, and distances measured along the scalp or in the brain.

The reference sections of relevant articles were checked for additional articles, and citations between included articles were recorded. 1384 initial results were decreased to 299 (22%) potential articles on the basis of titles and abstracts. PDFs of 291/299 (97%) were retrieved and inspected for relevant methods.

Inclusion criteria were experimental reports including TMS targeted over human S1. We restricted the analyses to TMS studies which either explicitly targeted the hand area of S1, used the hand area of M1 as a reference-point, or did not explicitly say which body part was targeted, but used the same methods as those studies which did target the hand area. For example, studies which positioned the TMS coil relative to a facial or foot muscle representation in M1 were excluded, but studies which positioned the TMS coil, for example over C3/C4, or over C3'/C4', or 2cm behind C3/C4, and which stated that this was over the 'somatosensory cortex' were included.

We excluded 12 review articles, 23 studies which targeted TMS over M1 or mapped M1, 48 studies which targeted other brain areas, 14 studies which did not report scalp coordinates, 41 studies which used other brain stimulation methods, 7 for other reasons, and 8 studies for which we could not access the full article. 14 additional studies from this search were excluded from the systematic review, but were relevant to the review of scalp-to-brain measurements, described below. 124/291 (43%) identified studies were included. 96/124 (77%) reported numerical coordinates for locating S1, met all other inclusion criteria, and are included in the analyses. We did not include or exclude studies based on the type of TMS equipment, experiment protocol, or participants tested – the purpose of the review was to identify the scalp locations stimulated, not the effects of stimulation on the brain or somatosensory perception.

Review of studies relating scalp and cortical anatomy

During the systematic reviews, fourteen articles were found which provided methods of relating scalp locations for the EEG electrode locations C3/C4 or TMS over M1, to anatomical landmarks or coordinates. No systematic search or review was attempted, however the reference sections of these articles was searched and followed for additional potential articles.

Systematic review of FMRI of S1-hand

PubMed was searched with the query "(primary somatosensory cortex OR S1 OR SI) AND (FMRI OR functional magnetic resonance imaging) AND (hand OR finger OR digit)" on the 7st January, 2018, and again on 31st July, 2018. 1252 search results were combined with 28 additional articles found in the previous search. This was reduced to 389 (31%) potential articles on the basis of titles and abstracts, searching for any neuroimaging methods and any somatosensory stimuli. A second, more thorough, review checked abstracts and/or full papers for inclusion criteria, which were: a) used FMRI, b) reported atlas coordinates in a standardized space (Talairach and Tournoux, 1988, or Montreal Neurological Institute, MNI), c) tested healthy adult human participants, d) applied somatosensory stimulation to the digit(s) or hand(s), and e) reported activation in the central sulcus, post-central gyrus, and/or any part of S1, using a statistical contrast between passive stimulation and no stimulation. 139/389 (36%) of studies were deemed relevant, but the full articles (.pdfs) were only available for 95 (68%) of the relevant articles. Of the 293 excluded articles, 142 (49%) did not report coordinates in 3 dimensions or reported coordinates only relative to other coordinates, 31 (11%) involved active hand movement, 30 (10%) did not use FMRI, 27 (9%) did not stimulate the hand, 25 (9%) contained data only from patients, children, or monkeys. The data from 4 further articles had been published elsewhere previously, 3 were purely anatomical studies, 3 were not in English, and 2 were not empirical studies. 26 (9%) were excluded because we could not access the full text.

The primary variable extracted from 95 selected articles was the reported 3D location of BOLD signal (peak voxel in group analysis, or mean across participants of peak voxel in individual analyses) in S1, including the body part targeted, the coordinate system used, and any anatomical or functional labels assigned to the coordinate. Means and standard deviations (SD) across participants were recorded or calculated where individual data were available. Coordinates reported using the Talairach and Tournoux reference system (most often, studies using BrainVoyager software) were transformed into MNI space. During analysis, and following advice from reviewers, we further restricted the analysis to coordinates which were labeled as being in BA3b, BA1, or BA2, and which were within the 50% cytoarchitectural probability maps of these three areas. The on-line data and analysis scripts include additional variables not explored in the present work, including stimulus modality (i.e., thermo/nociceptive, electrical, vibrotactile, brushing, and punctate stimulation).

Limitations

Due to limitations on time and resources, we did not use multiple independent databases for the systematic reviews, and we did not use multiple independent coders to select articles from the 2,636 identified records or to extract the stimulation and activation data from the 219 included papers. For the TMS literature search, we tracked the citations of all articles identified in order to locate studies not found by the initial searches. This did not lead to any additional articles. We did not, therefore, repeat this search for the FMRI literature. Because we included all stimulus sub-modalities in our FMRI literature search, the resulting mean coordinates for S1-hand may not be sufficiently precise for future researchers interested in only one somatosensory sub-modality. To address these limitations, we have provided all our data and analysis scripts in supplementary on-line materials. We encourage other researchers to validate, extend, and improve our work, for example by implementing a more thorough literature search with multiple independent searchers (e.g., Hayward et al. 2016), or by repeating the analyses using only their preferred sub-modality of stimulation.

Analysis

For all reported and measured scalp locations (lateral and anterior to the given reference point), and for reported FMRI coordinates (x, y, z), the means and standard deviations across studies were calculated, aggregating data across conditions where relevant. For FMRI studies which reported individual participants' coordinates, the mean across the individual coordinates was calculated within each study, separately for different brain areas (BA3b, BA1, BA2). Coordinates that were reported in Talairach (& Tournoux) space were converted into MNI space. Coordinates which were not reported as being in Talairach or MNI spaces were assigned to the most likely space, according to the software used (e.g., MNI for SPM, Talairach for BrainVoyager), or else plot in 3D alongside all other MNI coordinates, both before and after applying the Talairach-to-MNI transform to identify the most likely space. If unsure, the data were assumed to be in MNI space. For calculation of 'weighted means' across studies, we multiplied the reported means by the reported number of participants, then divided the sum of these values across all studies by the grand total of all participants across all studies, to give a weighted mean location, either on the scalp or in MNI coordinates.

Results and statistical analyses

Measurements of scalp size and 10:20 locations

Across 101 participants, the mean±SD head size was 35.9±2.1cm (range: 31-41cm) from nasion to inion, and 35.9±1.5cm (range: 33-40cm) between left and right pre-auricular points. This places the mean±SD C3/C4 electrode sites, on average, 7.2±0.3cm (range: 6.6-7.8cm) lateral to the vertex (Figure 1). Forty-four participants' heads were measured more than once (range 2-23 measurements; mean±SD=5.1±4.7 measurements per participant). Of these, the head measurements varied within-participants and between-sessions, by as much as 5cm for nasion to inion (mean±SD within-participants range=1.8±1.4cm), and 4cm for pre-auricular distances (mean±SD=1.3±0.9cm). The large range of these measurements is likely due to human error.

TMS over M1-FDI

Across 108 measurements from 56 participants, the mean±SD left hemisphere scalp *location of M1-FDI was 5.2±0.8cm left of, and 0.4±0.9cm anterior to the vertex (Figure 1). In 19 measurements from 14 participants, the mean±SD right hemisphere M1-FDI location was 5.2±0.9cm right of, and 0.5±0.9cm anterior to the vertex.*

Systematic review of TMS over S1-index

TMS studies targeting S1-hand have used three main localization strategies. The first study (Cohen et al. 1991) applied the border of a round coil, or the center of a figure-of-eight coil over the C3/C4 electrode location. This method was followed by Seyal et al. (1992, 1993), Pascual-Leone and Torres (1993), Siebner et al. (1998) and Harris et al. (2002). Starting with Enomoto et al. (2001), other studies also used C3/C4 as a reference point, but moved the coil posteriorly by between 2 and 3.6cm. In total, 16 studies used C3/C4 as a reference, and positioned the coil a mean±SD of 1.5±1.2cm posterior to C3/C4 (Table 1).

The second, and most common, strategy was to use the functionally-defined scalp location for a muscle in the hand (typically FDI, abductor pollicis brevis, APB, or opponens pollicis, OP) as a reference point. Starting with Sugishita and Takayama (1993), 43 such studies used MEPs to localize M1-FDI, then moved the coil posteriorly from that point on the scalp, by between 0 and 3cm (mean±SD=1.9±0.9cm). 16 additional studies used thenar muscles (APB, OP) to locate S1 (mean±SD=2.1±1.0cm posterior). 21 studies did not report using MEPs, but relied instead on visible twitches in the muscles of the hand (e.g., Amemiya et al. 2017). These studies moved the coil a mean±SD of 1.6±1.2cm posterior to the M1 hand area. In most studies, the researchers reported moving directly posterior (parasagitally) to the motor location, while other researchers moved at an oblique angle away from the midline, reasoning that the central sulcus is oriented at approximately 45 degrees to the midline (e.g., Balslev et al. 2004). The estimated mean locations stimulated under these different strategies are depicted in Figure 1. These estimates used data about the likely scalp locations of M1-FDI and C3/C4 obtained in our laboratory. These data are described below.

[FIGURE 1 ABOUT HERE]

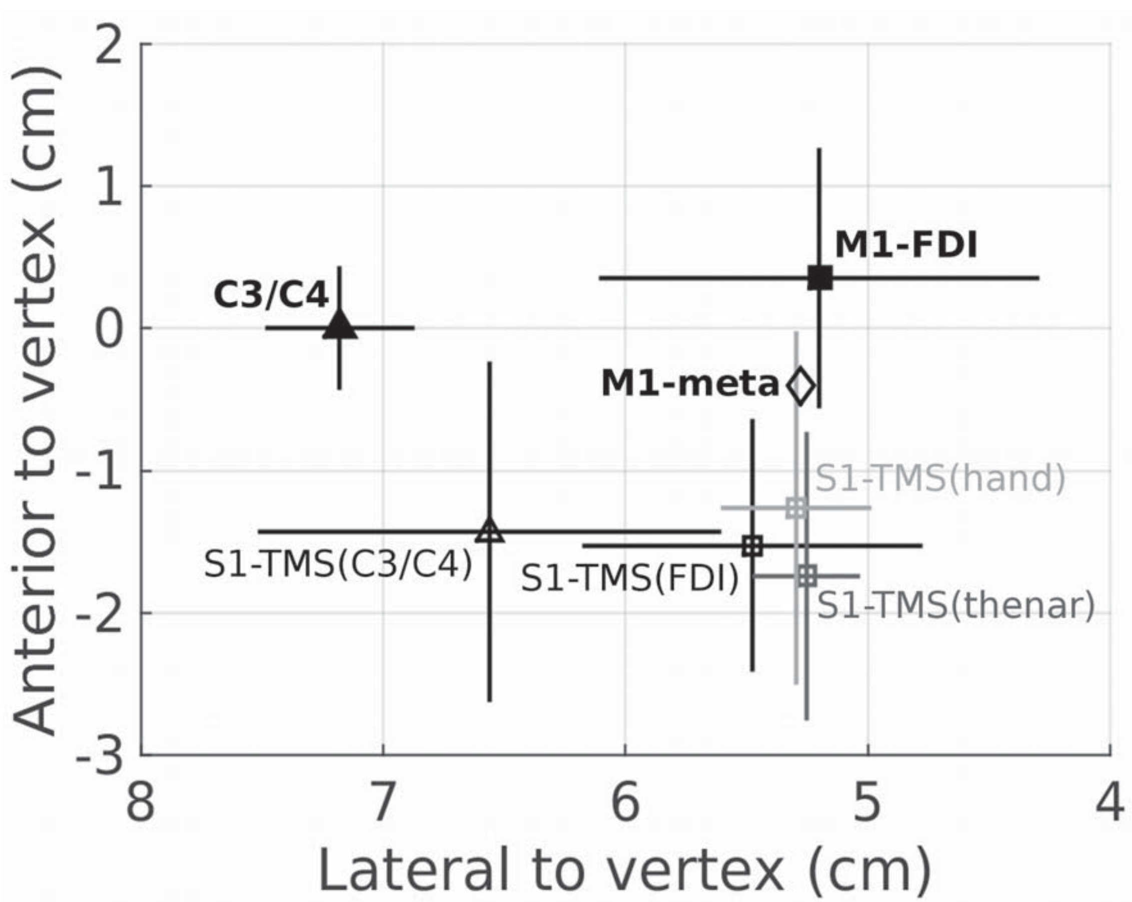

Figure 1. Systematic review of the locations stimulated in transcranial magnetic stimulation (TMS) studies of the hand area of primary somatosensory cortex (S1).

The grid shows locations lateral to the vertex, Cz(0,0) on the x-axis, and anterior to the vertex on the y-axis. The data points show mean±standard deviation (SD) locations measured or stimulated across the included studies (Table 1). Filled black square: Scalp location of primary motor cortex (M1) representation of the first dorsal interosseus (FDI) muscle of the hand, obtained from the HandLab database. Filled black triangle: Scalp location of the C3/C4 electroencephalographic electrode location obtained from the HandLab database. Black open triangle: Scalp location stimulated in TMS studies of S1 which use C3/C4 as a reference point (Table 2). Black open diamond: Scalp location of M1-FDI/thenar representation, obtained from non-systematic review (Table 3). Black open square: Scalp location stimulated in TMS studies of S1 which use the M1-FDI location as a reference point. Dark grey open square: Scalp location stimulated in TMS studies of S1 which use the M1-thenar location as a reference point. Light grey open square: Scalp location stimulated in TMS studies of S1 which use the M1 hand location (in general, usually without electromyography) as a reference point.

A third approach to locate S1-hand has been to use MRI-guided neuronavigation. This was done in three main ways: Using a standard head and brain template and registering each participant's head to the template head (4 studies, e.g., Ruzzoli and Soto-Faraco, 2014), using individual structural MRI scans obtained from each participant (7 studies, e.g., Romaiguère et al. 2005), using individual structural MRI scans with additional individual FMRI data (3 studies, e.g., Valchev et al. 2015). Seven additional studies reported using neuronavigation, but it was either not clear which of these three categories they used, or multiple approaches were used across different sub-groups of participants. Only one study that used neuronavigation also reported coordinates of S1 relative to M1 (Tamè and Holmes, 2016).

Review of studies relating scalp and cortical anatomy

In an appendix to a report on clinical EEG methods, Jasper (1958) reviewed four existing systems of EEG electrode positioning, and consolidated them into the 'Ten twenty' system of the International Federation. Cadavers and X-ray were used to register the EEG locations to the underlying brain anatomy. Positions C3/C4 are shown lying over the Rolandic fissure (see figure 6 in Jasper, 1958). Using MRI in 4 participants, Towle and colleagues (1993) found C3/4 to be anterior to the central sulcus in five hemispheres, and posterior in three. They reported that the location C3'/C4' (also called CP3/CP4), which is several centimeters posterior to C3, was posterior to the central sulcus in all participants. Three later studies (Lagerlund et al. 1993; Vitali et al. 2002; Okamoto et al. 2004) used MRI in 10 or more participants. All found that the brain underneath the C3/C4 location corresponded to the range of coordinates MNI(±51:57,-13:-23,54:58), with a left hemisphere weighted mean of MNI(-53,-18,57). The grey matter closest to this coordinate (e.g., MNI(-53,-17,55)) corresponds in the Harvard-Oxford and Juelich (e.g., Eickhoff et al. 2005) probabilistic atlases to postcentral gyrus (62%), BA1 (88%), BA2 (4%), BA3b (2%), BA4p (1%), and BA4a (1%). Finally, Xiao et al. (2018) published the most detailed and systematic mapping study to date, involving 114 Chinese and 24 Caucasian participants. C3/C4 is positioned just posterior to the central sulcus, over the postcentral gyrus. These studies are summarised in Table 2.

Seven studies were found that mapped the locations of M1-FDI or M1-APB to the scalp and/or cortical surface. Excluding a single case study which produced a very different localization, the M1-FDI/ABP location was found to be at Cz(-5.9:-4.8,-0.8:0.5), approximately 5cm lateral to the vertex (Figure 1). Three studies registered the optimal location for M1-FDI/APB to the cortical surface, finding the cortical projection point at MNI(-40:-31,-22:-14,52:59), with a weighted left hemisphere mean of MNI(-38,-15,58). This coordinate corresponds in the Harvard-Oxford and Juelich probabilistic atlases to precentral gyrus (38%), postcentral gyrus (2%) BA6 (50%), BA4a (38%), BA3b (19%), BA1 (9%), and BA4p (4%). These studies are summarised in Table 3.

Systematic review of FMRI of S1-hand

Of ninety-five studies reviewed, there were 216 reported coordinates relating to passive stimulation of the fingers, hand, and median nerve at the wrist. Some studies labeled the coordinates according to the likely Brodmann's areas (BA3b, BA1, BA2), but the majority used labels S1, SI, or postcentral gyrus. Juelich probabilistic atlases for BA3b, BA1, and BA2, in 1mm isotropic resolution in MNI152 space, were imported into Matlab. These maps had been thresholded at 50% likelihood for each brain area. The coordinates of the included studies were plot in 3D to check the distribution of data. Datapoints that were more than 2mm outside the 50% probability volumes were excluded. All remaining data were included. Averages for different hemispheres and reported Brodmann's areas are provided in Table 4, and a visual representation of the data is given in Figure 2. A full list of included studies, 3D figures, and all analysis data and scripts is available at https://osf.io/c8nhj/.

[FIGURE 2 ABOUT HERE]

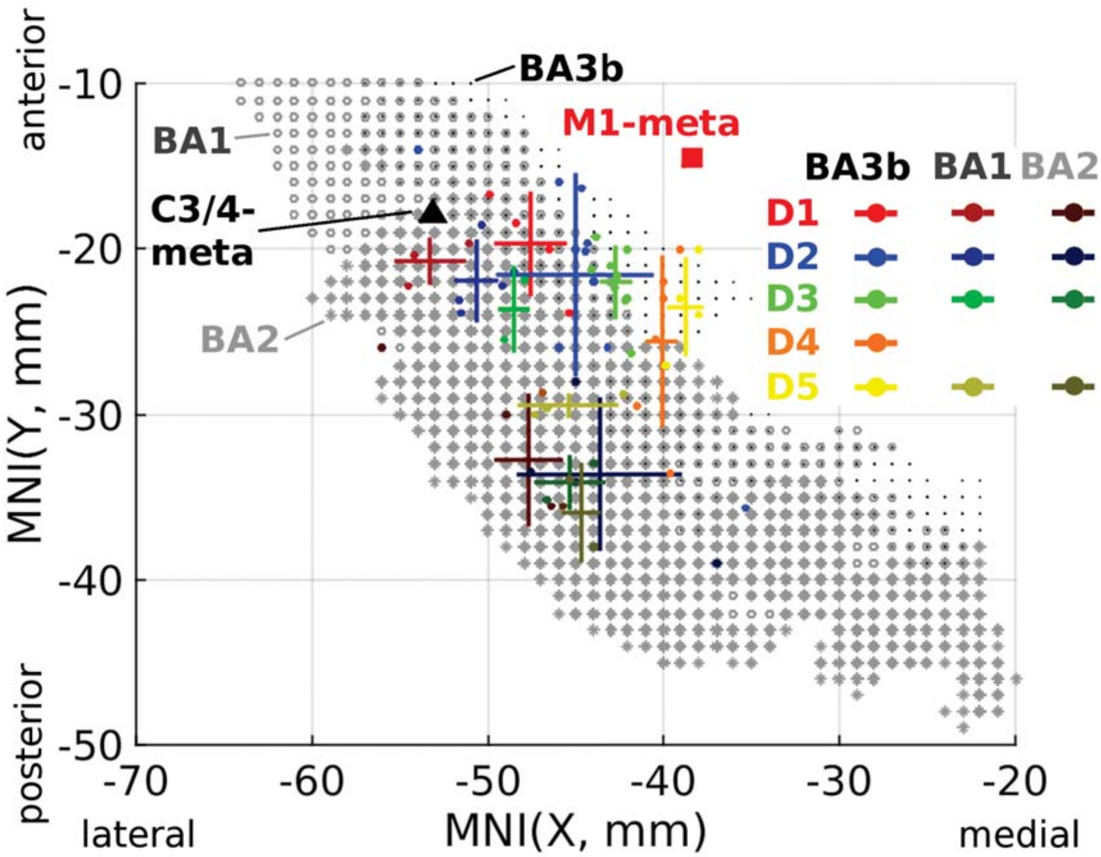

Figure 2. Systematic review of the locations activated in functional magnetic resonance imaging (FMRI) studies of the hand area of primary somatosensory cortex (S1-hand). The data show locations in the standard Montreal Neurological Institute (MNI) coordinates, with mm right of the origin shown on the x-axis, and mm anterior to the origin on the y-axis. The small background symbols show the 50% probability volumes of the Juelich cytoarchitectural maps for S1: Black dots: Brodmann's area (BA) 3b, open dark grey circles: BA1, light grey asterisks: BA2. Large filled symbols show the locations of C3/C4 (filled black triangle) and primary motor cortex (M1) representation of the first dorsal interosseus (FDI) or thenar muscle (filled red

square), obtained from the systematic reviews. Filled colored circles show the reported MNI coordinates of individual studies included in the review, separated by cytoarchitectural area. Different colors show different digits (D1: red, D2: blue, D3: green, D4: orange, D5: yellow). The lightest tones are for BA3b data, mid-tones for BA1, and darkest tones for BA2. Horizontal and vertical colored lines show the means±standard deviations (SD) of the data, by digit and cytoarchitectural area. Data for the ring finger (D4) were reported only for BA3b. The key result is that the blue crosses are lateral to the red square – that S1-index is lateral, not directly posterior, to M1-FDI.

Relationship between TMS locations and FMRI locations of S1-hand

Review of previous attempts to relate scalp and cortical anatomy revealed that the C3/C4 electrode location overlies the central sulcus, precentral gyrus, or postcentral gyrus, with a weighted mean coordinate for the cortical projection site of MNI(-53,-18,57). This site is 8mm lateral, 4mm anterior, and 7mm superior to the BA3b representation of S1-index, as determined by the systematic review. The scalp location of M1-FDI/APB across four studies was Cz(-5.3,0.0), and the likely cortical projection site was MNI(-38,-15,58). This is 7mm medial, 7mm anterior, and 8mm superior to the BA3b representation of S1-index.

The systematic reviews revealed very consistent strategies used to locate S1-index in TMS studies, namely moving an average of approximately 2cm posterior from M1-FDI. The systematic reviews also revealed that the cortical location of the index finger in FMRI studies of BA3b is likely 7mm lateral, 7mm posterior, and 8mm inferior to the cortical location of M1-FDI. The representation of the index finger in BA1 is likely 13mm lateral, 6mm posterior, and 8mm inferior to M1-FDI; and the index finger in BA2 is likely 5mm lateral, 18mm posterior, and 4mm inferior to M1-FDI. These distances are all measured within the brain. It is not yet known how these distances will convert to measurements taken from the scalp, nor how they relate to the optimal TMS coil position required to target S1-hand. These questions will be answered in a separate report.

Discussion

We systematically reviewed studies using transcranial magnetic stimulation and functional magnetic resonance imaging that targeted the hand area of the primary somatosensory cortex (S1-hand). Of 124 published TMS studies, the majority have used a heuristic to find S1-hand that involved finding the optimal location for stimulating the hand muscles (M1-hand), then moving the coil posteriorly, by a mean of approximately 2cm. Our own data, along with a review of similar studies (e.g. Sparing et al. 2008), shows that the optimal location for stimulating the M1 representation of intrinsic hand muscles is approximately 4-6cm lateral and 0-1cm anterior or posterior to the vertex. For primary somatosensory cortex, on average, TMS studies targeting the hand area of S1 have therefore stimulated a location ~6cm lateral, and ~1.5cm posterior to the vertex (Figure 1).

FMRI studies have localised the index finger representation of Brodmann’s BA3b in the left hemisphere at MNI(-45,-22,50), and of BA1 approximately 6mm lateral to that, at MNI(-51,-21,51). By co-registering data on the scalp position of M1-hand (M1-

meta in Figure 2) and C3/C4 into the same coordinate frame (i.e., the MNI template), the estimated locations of M1-hand and S1-hand can be compared. There is an orderly progression of the mean representation of the digits, with the little (D5) and ring finger (D4) representations in BA3b approximately 15mm posterior to M1-hand, and the thumb representation (D1) approximately 9mm lateral and 5mm posterior to M1-hand. These meta-analytic locations correspond well with the orderly topographies found within individual participants (e.g., Nelson & Chen 2008).

The heuristic of moving the TMS coil directly posterior to the M1 representation of the intrinsic hand muscles to locate the S1-hand representation therefore seems to be sub-optimal. This strategy is likely to be approximately correct if the TMS target is the BA3b representation of the little and ring fingers, but these digits are rarely targeted (only two out of the 87 reviewed studies that presented tactile stimuli to the fingers targeted these digits – Amassian et al. 1991; Knecht et al. 2003). By contrast, the largest number of studies used the M1 representation of intrinsic hand muscles to target the S1 representation of the index finger (36 of the 87 studies presented tactile stimuli on the index finger). Despite the predominance of this strategy, the systematic review data suggest that S1-index is lateral and slightly posterior to M1-hand.

The conclusion that S1-hand is lateral to M1-hand is supported by studies in which both M1 and S1 representations are measured together. Blatow and colleagues (2011) applied passive pneumatic stimulation to the index finger and thumb of 16 participants, as well as asking them to make finger-thumb opposition movements for digits 1-5. The peak BOLD response in their active movement task (after converting their coordinates to MNI space) puts M1-hand at MNI(-39,-29,58), and S1-hand in the sensory task 11mm laterally, 2mm anteriorly, and 6mm inferiorly, at MNI(-50,-27,52). Their figure 2b clearly shows S1-hand lateral to M1-hand. Similar conclusions were reached by Schellekens et al. (2018) using population receptive field methods, and by Tamè & Holmes (2016), who reported that the S1-index representation was 11mm lateral, 7mm posterior, and 11mm inferior to the M1 representation of FDI, as measured using TMS-evoked MEPs in that muscle.

Given that moving the TMS coil posterior to the M1-hand representation does not seem optimal to target S1-hand, the question arises as to why this method seems to have become the default. Indeed, this method is still commonly relied upon, with one recent paper stating: "*A large body of evidence shows that the hand area in the somatosensory cortex can be successfully targeted by positioning the coil 1–4 cm posterior to the motor hotspot*" (Gallo et al. 2018, p19). The earliest TMS studies of S1 (e.g., Cohen et al. 1991; Seyal et al. 1992, 1993) positioned the TMS coil over the C3/C4 electrode position. These studies presumably relied on evidence showing that the C3/C4 location lay approximately over the central sulcus (Jasper, 1958; Towle et al. 1993; Table 2). Indeed, studies relating the C3/C4 position to the underlying brain surface gave an estimated location of the C3/C4 projection point of MNI(-53,-18,57) (Figure 2). This cortical projection point of C3/C4 is just 6.6mm from the BA1 representation of the thumb.

Since the C3/C4 projection point is so close to the likely representation of thumb and index fingers in BA1 and BA3b, and the available evidence suggests that finger representations in S1 are lateral to those in M1, why is *2cm posterior to the M1-hand location* the dominant reference point for TMS studies of S1-hand? While the literature is not clear on this point, one possibility is that, following Towle et al. (1993), who reported that the C3'/C4' electrode location was posterior to the central sulcus in all four of their participants, subsequent researchers have used C3'/C4' to ensure that they were on the posterior side of the central sulcus. C3'/C4' (also labeled CP3/CP4) is halfway between C3 and P3, which, from our scalp measurements is about 3.6cm posterior to C3/C4. Relatively few studies have used a site as posterior as this to target S1 (e.g., McKay et al. 2003; Restuccia et al. 2007). Other researchers have located C3'/C4' only about 1.5cm posterior to C3/C4 (Pascual-Leone & Torres, 1993). Some researchers state that the C3/C4 location is several centimeters posterior to the optimal location to stimulate M1 (Feurra et al. 2011; Koch et al. 2006; McKay et al. 2003; Nardone et al. 2015, 2016), which from our scalp measurements does not seem correct. Other researchers state that C3/C4 is the approximate scalp location of the M1-hand representation (e.g., Fiorio & Haggard 2005; McKay et al. 2003). It seems that, at some point, the original heuristic of 'posterior to C3/C4' has changed into the heuristic 'posterior to M1-hand'. We did not find an empirical justification for this change. At present, then, selective citation of the literature can be used to justify a number of different strategies. In systematically reviewing this literature, it is clear that there is very little agreement among researchers about the relative scalp locations of C3/C4, C3'/C4', and their relationship to the underlying representations of M1-hand, and S1-hand. The data reviewed here show that these areas are all several centimeters apart. In the following, we consider two additional reasons why researchers might have chosen to move the TMS coil posteriorly from M1-hand to target S1-hand.

Using TMS to evoke MEPs in hand muscles provides a potentially very reliable functional localiser for M1-hand. Localising M1-hand functionally is likely better than relying on scalp measurements alone. Once M1-hand has been localised, researchers have often justified moving the coil posteriorly to M1-hand in order to ensure that muscle twitches evoked by stimulating over M1 would not interfere with the intended effects of TMS over S1 (e.g., Convento et al. 2018; see also Holmes & Tamè, 2018). This strategy can be criticized on two grounds.

First, M1 and S1 are adjacent and anatomically contiguous in the brain. For the purposes of TMS, stimulation of the posterior bank of the precentral sulcus (e.g., BA4p, primary motor cortex) and the anterior bank of the postcentral sulcus (e.g., BA3b, primary somatosensory cortex) is very likely to occur simultaneously. Selective stimulation of particular sub-areas of primary sensory (e.g., BA3a vs. BA3b) or motor cortex (BA4a vs. BA4p) is likely to require detailed and careful work to optimise precisely the necessary location, orientation, intensity, and TMS pulse pattern (e.g., Hamada et al., 2012). By comparison to the strategy for selectively stimulating S1 but not M1, TMS studies focusing on M1 (or other brain areas) have not argued for moving the coil anteriorly in order to prevent simultaneous stimulation of S1, even though it is likely that S1 stimulation directly affects M1 activity, for example, as shown by the short-afferent-inhibition paradigm (Tamè et al. 2015; Turco et al. 2018). Rather, specific stimulation of M1 must be deduced from the effects of TMS, and these may depend on the timing, intensity, orientation, or pattern of TMS impulses, on connectivity with other areas, or on other factors that allow M1 involvement to be determined.

Second, in our previous experiments using FMRI-guided neuronavigated TMS over S1, while TMS has indeed evoked muscle twitches in many participants, the amplitude of these twitches did not correlate with the effects of TMS on tactile perception (Tamè and Holmes, 2016). We suggest that there is no necessary reason to attempt to avoid the side-effects of M1 stimulation when targeting S1. Rather, researchers should stimulate S1 as directly as possible, measure any muscle contractions that result, and test whether these contractions interfere or correlate with somatosensory perception or other measures. To this end, it may be that different coil orientations should be used to stimulate S1-hand as compared to M1-hand (e.g,. Pascual-Leone et al. 1994; Raffin et al. 2015). Future studies will need to follow-up on these reports of the optimal coil orientation for interfering with somatosensory perception. Once we are more certain about the location of S1-hand, we can then begin to study how S1-hand and somatosensory perception respond in detail to systematic changes in TMS coil position and orientation, and TMS pulse intensity, frequency, and pattern.

It may also be argued that, by moving the TMS coil 2cm posterior to M1-hand, researchers were specifically targeting the little or ring finger representations in BA3b or BA1, or the largely-overlapping finger representations in BA2 (Figure 2). 2cm directly posterior to M1-hand (i.e., MNI(-38,-35,58) – compare the location stimulated by Ku et al. 2015: MNI(-34,-36,51)) is likely on the posterior bank of the postcentral gyrus (cytoarchitectural probability: 39%) or superior parietal lobule (17%), and may include parts of BA3b (52%), BA2 (46%), BA1 (21%), BA7 (20%), BA4p (12%) BA5 (5%) or BA4a (4%). BA1 and BA2 are less clearly somatotopically organized than BA3b (Martuzzi et al. 2014; see Figure 2). It is therefore possible that TMS over a region approximately 2cm behind M1-hand may be sufficient for targeting higher-order and less topographic representations of the hand in S1. Although we have not done the necessary systematic review or experiments to determine which part of S1 is 2cm posterior to the M1-hand location, it is most likely to be a part of S1 that represents the forearm, upper arm, and/or shoulder (e.g., Blankenburg et al., 2006; Figure 2).

Scope and recommendations

This review was limited to assessing the scalp locations that previous TMS studies have assumed to correspond to S1-hand, as well as the brain locations activated during passive somatosensory stimulation of the hand. Explicitly relating the TMS scalp measurements and the FMRI brain measurements is beyond the scope of this review. In an accompanying experimental paper (Holmes et al., under review), we systematically map the effect of TMS on tactile perception, provide a probabilistic atlas of the central sulcus, and systematically measure the location of S1-hand using individual FMRI-guided neuronavigation. From the systematic reviews reported here, we can make three general recommendations.

First, we recommend that all TMS studies should use as much of the available evidence as possible to guide and justify their choice of target scalp locations, including systematic review, meta-analysis, FMRI, M/EEG, scalp measurements, and behavioral data. By selectively citing the literature, quite a wide range of strategies for localising a TMS target can appear evidence-based. In the reviewed literature, we were unable to find any empirical evidence to support the most commonly-reported strategy for localising S1-hand in TMS studies, that is, moving 2cm posterior from the M1-hand representation. While the distances involved are relatively small (i.e., 2cm, relative to a typical TMS coil diameter of 7cm), researchers studying MEPs elicited by TMS over M1 know just how sensitive the measurements can be to relatively small changes in TMS coil position and orientation. More accurate positioning of the TMS coil should increase the effect sizes of the phenomena we set out to measure.

Second, we recommend that all TMS studies systematically measure and report their participants' head measurements and the scalp locations stimulated, using a common reference frame. Very few studies reported scalp measurements. For sites close to the vertex, measurements lateral and anterior in a Cartesian system relative to the vertex may be sufficient, although a polar system may be superior. For sites further from the vertex, the reference point could be relative to another 10:20 electrode location (e.g., C3/C4; Pz). If a functional localiser is available, such as MEPs elicited from M1-FDI, then careful mapping of that functional location is required prior to reporting the target location relative to that reference.

Finally, from the evidence presented here, we suggest that the representation of the index finger in BA3b and BA1 is likely to be around 1cm lateral, and 0.5cm posterior to M1-FDI, as measured in the brain. These distances, particularly the lateral distance, are likely to be underestimates relative to the equivalent distances measured along the scalp, due to the distance between the scalp and the brain, and the curvature of the scalp. The scalp localisation of S1-index is addressed by Holmes et al. (under review).

Online data

Raw data, supplementary results, data sheet, (https://osf.io/c8nhj/).

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Table 1: Systematic review of approximate scalp locations stimulated in 117 TMS studies of S1-hand

		Relative to Reference (cm)		Relative to Cz (cm)†	
Reference	**N***	**Lateral**	**Anterior**	**Lateral**	**Anterior**
C3/C4	16	0.0±0.0 (0.0:0.0)	-1.5±1.2 (-3.6:0.0)	-6.6±0.9 (-7.2:-5.2)	-1.4±1.2 (-3.6:0.4)
FDI	43	-0.3±0.7 (-3.0:0.0)	-1.9±0.9 (-3.0:0.0)	-5.5±0.7 (-8.2:-5.2)	-1.5±0.9 (-2.7±0.4)
Thenar	16	-0.1±0.2 (-0.9:0.0)	-2.1±1.0 (-4.0:0.0)	-5.3±0.2 (-6.1:-5.2)	-1.7±1.0 (-3.7:0.4)
Hand/other	21	-0.1±0.3 (-1.0:0.0)	-1.6±1.2 (-4.0:0.0)	-5.3±0.3 (-6.2:-5.2)	-1.3±1.2 (-3.7:-0.4)
Navigated‡	21	-	-	-	-

Data are Means±SD (min:max). * Number of studies. Location data are not weighted by study sample-size. † Approximate measures, based on estimated population means reported below; **‡** Most neuronavigated studies did not report any coordinates, so no summary data are available.

Table 2: Nonsystematic review of C3/C4 location

Study	Methods	N	C3/C4*
Jasper 1958	Cadavers, X-rays	?	Over CS
Towle et al. 1993	MRI-EEG	4	Anterior to CS (5 hemispheres) Posterior to CS (3 hemispheres)
Lagerlund et al. 1993	MRI-EEG	10	45.6° lateral from Cz
Vitali et al. 2002	MRI-EEG	10†	M=MNI(-57,-13,54) SD=MNI(5,13,6)
Okamoto et al. 2004	MRI-EEG	17	M=MNI(-53,-16,58) SD=8; over postcentral gyrus
Koessler et al. 2009	MRI-EEG	16	MNI(-51,-23,57)‡
Cutini et al. 2011	MRI-EEG	(model)	MNI(-53,-11,49)
Xiao et al. 2018	MRI-EEG	114+24	Postcentral gyrus

C3/C4: anatomical location(s) of this electrode position; CoG: center of gravity; CS: central sulcus; Cz: vertex; M: Mean; MNI: Montreal Neurological Institute 152 template brain; N: Number of participants or brains; SD: Standard Deviation. * Right hemisphere X-coordinates, if given, were inverted and averaged with left hemisphere (left-right differences were minimal); † Patients with epilepsy. ‡ Converted from Talairach and Tournoux coordinates.

Table 3. Non-systematic review of M1-Hand scalp and brain location

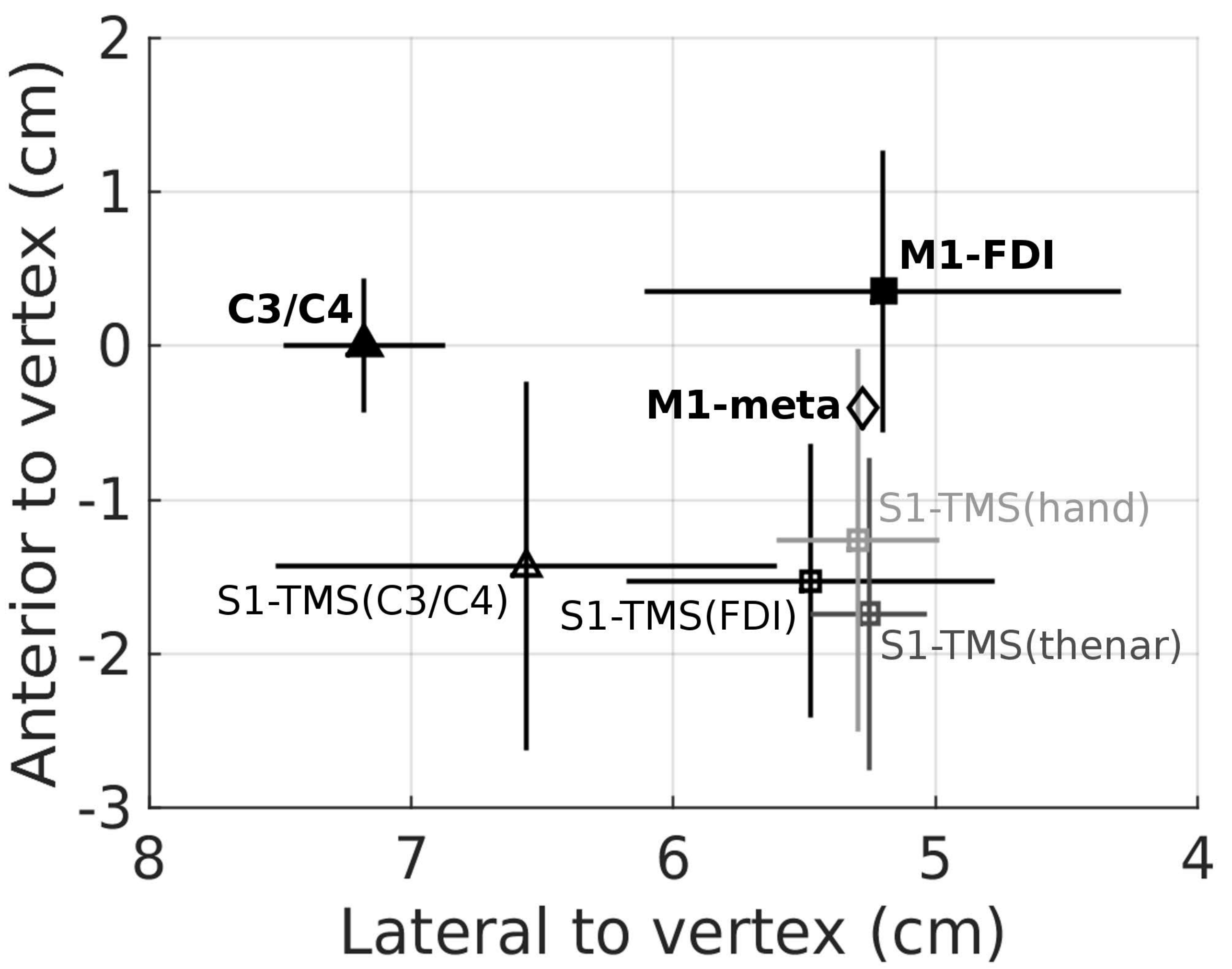
Study	TMS Methods	N	M1*
Wilson et al 1993	M1-APB CoG M1-ADM CoG	10	Cz(-5.9,0.5) Cz(-5.4,0.4)
Ruohonen et al 1996	MRI-MEG-TMS M1-APB M1-ADM	1	Precentral gyrus Cz(-3.0,2.0)
Boroojerdi et al 1999	FMRI-TMS M1-APB/FDI	4	Cz(-5.5,0.25)
Borghetti et al 2008	M1-ADM Median M1-ADM CoG	10	Cz(-4.5,0.0) Cz(-4.9,-0.8)
Sparing et al 2008	(Meta-analysis) M1-FDI Max	10	MNI(-31,-22,52) Cz(-4.8,-0.8)
Niskanen et al 2010	M1-APB	59	MNI(-38,-14,58)
Raffin et al 2015	MRI, M1-FDI	13	M=MNI(-40,-17,59) SD=MNI(10,7,24)

Cz: vertex; M: Mean; MNI: Montreal Neurological Institute 152 template brain; N: Number of participants or brains; SD: Standard Deviation. * Right hemisphere X- coordinates, if given, were inverted and averaged with left hemisphere (left-right differences were minimal); CoG: Centre of Gravity

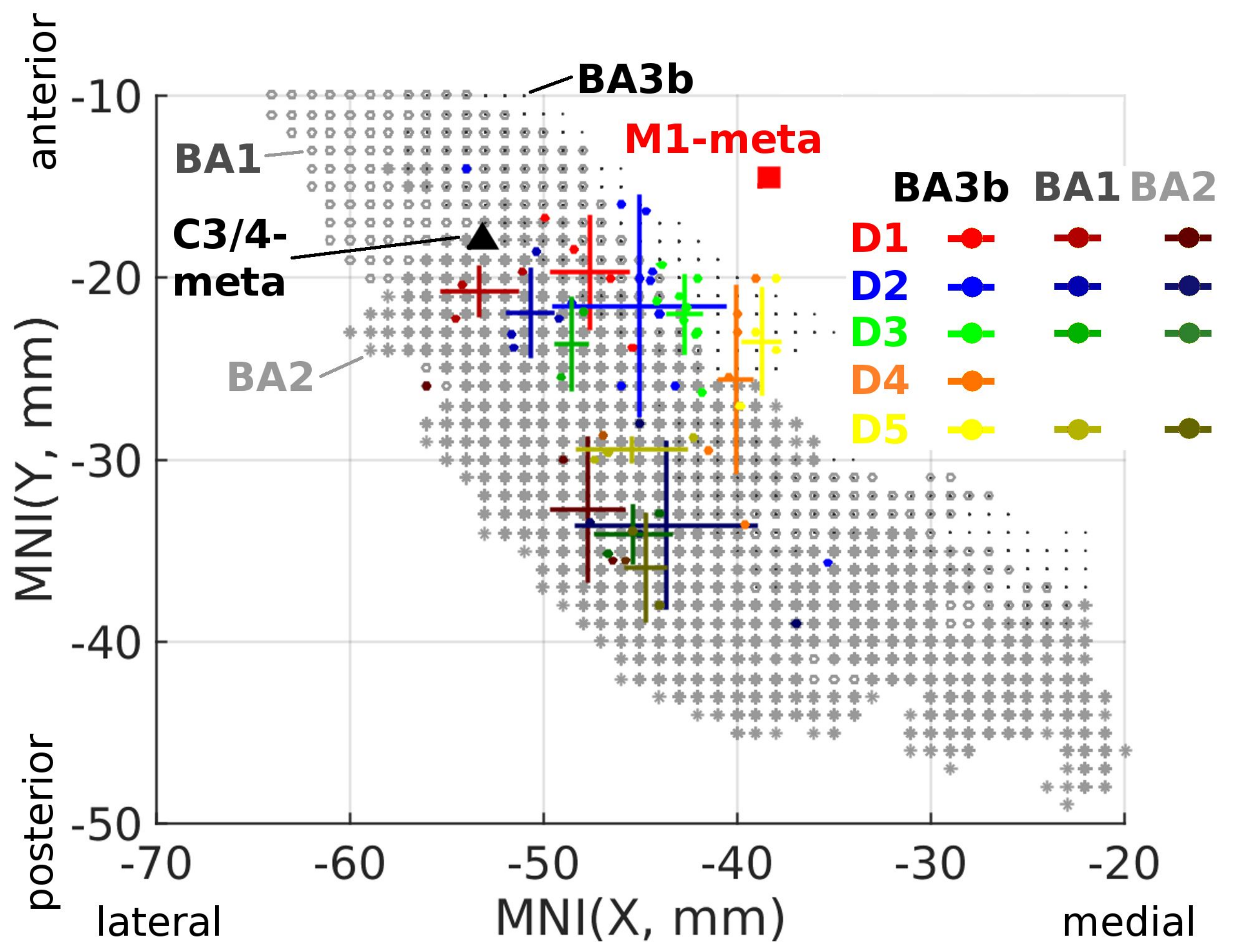
Table 4: Weighted mean±SD reported S1 MNI coordinates across the reviewed studies

Body	BA	Hem	N datapoints				MNI Coordinate means and SDs								
			Studies		People		X			Y			Z		
			Ms	SDs	Ms	SDs	M	SD_M	SD_P	M	SD_M	SD_P	M	SD_M	SD_P
Thumb (D1)	3b	L	4	4	52	52	-48.0	1.96	7.00	-19.0	3.04	4.27	47.3	3.25	6.25
		R	4	4	58	58	47.4	1.70	3.84	-18.3	2.81	2.86	45.7	0.25	3.79
	1	L	3	3	37	37	-52.8	1.92	2.41	-20.5	1.33	4.17	50.9	2.66	3.57
		R	6	5	98	61	53.9	3.40	3.28	-19.4	3.66	3.76	50.4	3.86	3.58
	2	L	2	2	9	9	-47.2	1.84	27.9	-33.9	3.89	5.42	56.5	4.53	7.13
		R	2	2	15	15	54.7	0.25	5.97	-24.8	2.43	4.60	48.5	1.29	5.74
Index (D2)	3b	L	11	5	136	81	-45.2	4.39	4.47	-21.6	6.00	2.87	49.8	5.30	4.52
		R	5	4	71	58	44.5	0.63	3.36	-19.9	3.41	2.98	50.0	1.00	2.93
	1	L	4	3	46	34	-50.8	1.14	2.01	-21.4	2.37	3.05	50.7	5.72	2.98
		R	6	4	105	52	50.1	3.58	2.50	-20.5	3.80	2.76	52.3	4.69	2.57
	2	L	4	1	83	6	-43.6	4.60	1.23	-33.3	4.50	1.06	53.8	6.33	1.23
		R	2	1	35	12	54.2	0.46	2.39	-21.0	4.07	2.50	49.3	0.52	3.70
Middle (D3)	3b	L	9	6	96	66	-43.0	0.84	3.26	-21.6	2.08	3.40	53.4	3.10	3.53
		R	4	4	58	58	43.5	0.44	3.91	-21.3	2.06	3.85	53.5	1.31	4.41
	1	L	2	2	28	28	-48.4	0.78	7.77	-23.2	2.47	3.22	56.1	5.23	4.65
		R	4	4	52	52	48.0	4.79	4.69	-22.2	5.25	5.26	54.3	5.65	5.13
	2	L	2	1	22	6	-44.7	1.91	2.00	-33.6	1.56	1.66	58.0	2.55	2.34
		R	1	1	12	12	53.7	-	3.90	-25.8	-	2.60	51.5	-	5.00
Ring (D4)	3b	L	6	3	75	45	-39.9	0.81	3.37	-27.4	5.09	4.15	55.3	4.23	2.60
		R	3	2	22	22	40.9	0.79	3.73	-26.9	2.41	4.23	58.4	1.35	3.34
	1	L	1	1	10	10	-46.9	-	2.10	-28.7		3.10	63.8	-	3.10
		R	3	3	34	34	48.0	5.57	5.21	-25.0	8.34	4.90	56.7	7.68	4.01
	2	L	1	1	6	6	-45.8	-	2.20	-35.6	-	3.50	62.1	-	3.40
		R	1	1	12	12	54.8	-	5.10	-24.5	-	3.90	49.6	-	5.80
Little (D5)	3b	L	4	0	40	0	-38.7	0.91	-	-23.5	2.89	-	55.5	3.88	-
		R	2	1	14	12	40.0	1.63	3.40	-27.8	0.18	3.36	59.5	5.35	3.47
	1	L	3	3	23	23	-45.7	2.78	3.58	-29.5	0.62	3.41	60.5	7.37	4.72
		R	3	3	31	31	45.5	7.09	4.92	-24.3	6.68	4.07	59.9	8.22	4.18
	2	L	2	1	9	6	-44.9	0.99	1.42	-35.3	2.90	4.03	59.1	5.37	4.27
		R	2	2	15	15	53.9	2.72	2.95	-24.6	5.85	5.08	48.6	2.28	5.16
Palm	3b	L	3	1	24	8	-37.2	4.07	2.48	-34.3	6.61	1.37	60.4	2.19	1.56
		R	1	0	12	0	40.4	-	-	-35.0	-	-	62.4	-	-
Back	3b	L	2	1	26	16	-42.9	5.60	2.20	-24.9	1.03	1.29	52.2	2.06	1.12
		R	1	1	16	16	44.3	-	1.32	-25.7	-	1.80	54.5	-	1.13
	1	L	1	1	16	16	-52.9	-	1.49	-22.9	-	2.18	52.4	-	2.31
		R	2	1	33	16	41.8	11.4	1.59	-28.8	7.60	1.26	64.9	10.4	0.86
	2	L	1	1	16	16	-49.1	-	3.64	-31.0	-	3.64	51.8	-	3.64
		R	1	1	16	16	49.9	-	3.64	-28.7	-	3.64	54.5	-	3.64

Hem.: Hemisphere; N: total sample size across studies; X, Y, Z: MNI coordinates; BA3b, BA1, BA2: Brodmann's areas; * Other areas in S1 or postcentral gyrus not given a BA label; MN: Median or radial nerve stimulation. M: Mean; SD_M: SD across study means; SD_P: SD across participants.



M1-FDI
C3/C4
M1-meta
S1-TMS(hand)
S1-TMS(C3/C4)
S1-TMS(FDI)
S1-TMS(thenar)
Anterior to vertex (cm)
Lateral to vertex (cm)
2
1
0
-1
-2
-3
8
7
6
5
4



anterior
posterior
MNI(Y, mm)
MNI(X, mm)
lateral
medial
-10
-20
-30
-40
-50
-70
-60
-50
-40
-30
-20
BA3b
BA1
BA2
M1-meta
C3/4-meta
BA3b
BA1
BA2
D1
D2
D3
D4
D5