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Title: Locating primary somatosensory cortex in human brain stimulation studies: Experimental 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) does not produce immediate outputs. Researchers must therefore rely on indirect methods for TMS coil positioning. The 'gold standard' is to use individual functional and structural magnetic resonance imaging (MRI) data, but the majority of studies don't do this. The most common method to locate the hand area of S1 (S1-hand) is to move the coil posteriorly from the hand area of primary motor cortex (M1-hand). Yet, S1-hand is not directly posterior to M1-hand. We localised the index finger area of S1-hand experimentally in four ways. First, we re-analysed functional MRI data from 20 participants who received vibrotactile stimulation to their 10 digits. Second, to assist the localisation of S1-hand without MRI data, we constructed a probabilistic atlas of the central sulcus from 100 healthy adult MRIs, and measured the likely scalp location of S1-index. Third, we conducted two experiments mapping the effects of TMS across the scalp on tactile discrimination performance. Fourth, we examined all available neuronavigation data from our laboratory on the scalp location of S1-index. Contrary to the prevailing method, and consistent with systematic review evidence, S1-index is close to the C3/C4 electroencephalography (EEG) electrode locations on the scalp, approximately 7-8 cm lateral to the vertex, and approximately 2 cm lateral and 0.5 cm posterior to the M1-FDI scalp location. These results suggest that an immediate revision to the most commonly-used heuristic to locate S1-hand is required. The results of many TMS studies of S1-hand need reassessment.
New and noteworthy

Non-invasive human brain stimulation requires indirect methods to target particular brain areas. Magnetic stimulation studies of human primary somatosensory cortex have used scalp-based heuristics to find the target, typically locating it 2 cm posterior to the motor cortex. We measured the scalp location of the hand area of primary somatosensory cortex, and found that it is approximately 2 cm lateral to motor cortex. Our results suggest an immediate revision of the prevailing method is required.

Keywords: S1, SI, TMS, TDCS, vibrotactile
1. Introduction

Transcranial magnetic stimulation (TMS, Barker et al. 1985) can be used to study the healthy human brain non-invasively, by stimulating brain tissue electromagnetically. TMS therefore requires indirect methods of locating the brain area of interest. Primary motor cortex (M1) can be located relatively easily, by moving the TMS coil around on the scalp, applying single pulses of TMS, and observing or recording muscle responses, however, for most other brain areas, there is no similar, immediate and objective output that researchers can use, on a pulse-by-pulse basis, to ensure correct TMS coil position. The 'gold standard' in this field is to acquire, for every participant, structural and functional brain imaging data and use frameless stereotaxy (Sparing et al. 2010).

When MRI is not available, researchers have used scalp-based heuristics to target the hand area of primary somatosensory cortex (S1-hand, Holmes & Tamè, in press; preprints available at: https://osf.io/c8nhj/). These heuristics have included using the 10-20 or 10-10 electroencephalographic system (Jasper 1958; Koessler et al. 2009; Lagerlund et al. 1993; Okamoto et al. 2004; Towle et al. 1993; Vitali et al. 2002; Xiao et al. 2018), functionally-identified scalp locations for motor cortex (e.g., Balslev et al. 2004), changes in reaction times or errors (e.g., Convento et al. 2018), or changes in sensation (e.g., Sugishita & Takayama 1993; Cowey & Walsh 2000). Systematic review revealed the most common heuristic involves positioning the coil 2 cm posterior to the M1 representation of hand muscles (e.g., first dorsal interosseous, FDI, or abductor pollicis brevis, APB), yet S1-hand is lateral, not posterior to M1-hand (Holmes & Tamè, in press). In previous work using individual FMRI-guided
neuronavigation (Tamè & Holmes, 2016), we noticed that, in all 20 of our participants, the scalp location above S1-index was indeed lateral, not directly posterior, to M1.

Here, we ask: “what is the optimal location on the scalp to magnetically stimulate the somatosensory cortex (Brodmann’s areas BA3b & BA1, Geyer et al. 1999) representations of the index finger (S1-index)? The index finger and the FDI muscles are the most commonly stimulated and recorded body parts in the relevant literature, respectively, so we focused on them. We focused on the BA3b and BA1 subregions of S1 because they show a clear somatotopy for individual fingers (Nelson & Chen 2008), because our FMRI protocol was not able to distinguish between them, and, for the purposes of applying TMS on the scalp, because the representations of each finger in BA3b and BA1 lie very close to each other (e.g., Figure 2 in Holmes & Tamè, in press). We answered the question in four ways: First, by re-analysing functional MRI data from our laboratory (Tamè & Holmes, 2016); Second, by creating a probabilistic atlas of the central sulcus from 100 structural MRIs, and measuring between-participant variability in central sulcus location at the likely position of S1-index; Third, by conducting two experiments which systematically mapped the effect of TMS on vibrotactile discrimination performance across the scalp, and; Fourth, by summarizing all our available data from individual (F)MRI-neuronavigated TMS experiments targeting S1-index. Together, these independent and converging lines of evidence strongly support the immediate revision of the most commonly-used heuristic for locating human primary somatosensory cortex in TMS studies.
**Materials and methods**

Studies were approved by research ethics committees (UREC11/58, University of Reading, UK; SoPEC916, University of Nottingham, UK), conducted in accordance with TMS safety guidelines (Rossi et al. 2009) and the Declaration of Helsinki (2008 version, which does not require pre-registration).

**Participants**

FMRI experiment: Twenty healthy participants (mean±SD age=27.6±8.7 years, 15 female, 3 left-handed by self-report). Structural MRI: 100 right-handed participants (mean±SD age=25.1±6.2 years, 64 female; Holmes et al., 2008; Tamè and Holmes, 2016, unpublished datasets). Experiment 1: nine participants (mean±SD age=33.2±11.6 years, 5 female, 1 ambidextrous; 13 were recruited, 4 were removed). Experiment 2: twelve participants (mean±SD age=23.7±5.6 years, 5 females, 12 right-handed). Participants met TMS safety inclusion criteria (Rossi et al. 2009), with no neuropsychiatric disorder. Neuronavigation: 37 localisations of S1-index from 15 participants, separately for left (N=11, mean±SD=25.4±6.1 years, 7 female) and right hemispheres (N=9, mean±SD=26.2±6.3 years, 3 female).

**Functional MRI data**

Data reported by Tamè and Holmes (2016) were re-analysed. Participants underwent 10x280 s scans, each comprising 10x11.5 s vibrotactile stimulation blocks interleaved with 10x12.5 s rest. Stimuli were produced by MRI-compatible piezoelectric wafers driving a 2.5 mm diameter plastic rod (~100Hz, 8x1 s, 0.5 s pause). One scan (Siemens Trio 3T, 3x3x3 mm) was collected for each digit on each hand, in
pseudorandomised order. FMRI data were processed with FSL5 (http://www.fmrib.ox.ac.uk/fsl): 3D spatial smoothing (5 mm FWHM), 6- and 12-degree-of-freedom linear registration to the anatomical (MPRAGE, 1x1x1 mm) and MNI152 (2x2x2 mm) template brains, respectively. Data were modeled as square-wave regressors convolved with canonical hemodynamic response functions. Two contrasts were made with each set of 10 scans: Single digit contrasts of vibration versus rest, within scans; Differential contrasts of each digit against the other four of that hand, across scans (e.g., left index finger (D2) contrasted against the left thumb (D1), middle (D3), ring (D4), and little (D5) digits, weights: [-1,4,-1,-1,-1,-1]). Group means were calculated for each digit and each contrast (20 group-level images). The voxel with maximum Z-score in postcentral gyrus of presumed primary somatosensory cortex of each group image was recorded. Harvard-Oxford and Juelich atlases (Eickhoff et al. 2005) within FSLView were used to assign probabilistic anatomical and functional labels to voxels.

Probabilistic atlas of the central sulcus, and S1-index scalp location

Structural MRI scans were used to create a probabilistic central sulcus atlas. The location of S1-index on the scalp was estimated by measuring seven points along the scalp between midline and the scalp overlying S1-index (MNI[-48,-21,50], Holmes & Tamè, in press). 112 scans (MPRAGE, 1x1x1 mm) were acquired from: Siemens Sonata 1.5T (N=43, University of Oxford, UK); Siemens Magnetom Trio 3T (N=20, University of Reading, UK), and Philips Achieva 3T (N=49, University of Nottingham, UK). 8 were excluded for self-reported left-handedness, 1 for scan quality (artefacts), and 1 for poor health (severe uncorrected visual deficits). 2 scans which did not
include the full scalp, nasion, and inion were also removed.

Each image was viewed in axial/transverse plane, by NPH or SZ. Using a 2 mm 'pencil', the complete bilateral course of the central sulcus was drawn on the image, starting at the hand knob, moving superiorly then inferiorly and laterally from the hand area. We filled all gaps between pre- and postcentral gyri to provide a liberal estimate of central sulcus location and width. Five landmarks were drawn on the images with 3x3x3 mm masks: nasion, inion, left and right pre-auricular points, vertex (Figure 1H).

Nasion and pre-auricular points were easily identified, but inion prominence varied greatly. Vertex was estimated by calculating a line orthogonal to and through the intersection of nasion-inion and pre-auricular lines, then using ruler and protractor to find the scalp location 90 degrees from the intersection. A best guess for vertex location was then taken, considering three image planes. It is not known how these locations correspond to those measured on participants' heads during S1-index TMS.

Participants' brain images were extracted using BET, and both head and brain were registered to MNI152 1x1x1 mm templates using FLIRT (12 degrees of freedom). The two transformations (head, brain) were applied to central sulcus mask images to create masks in standard MNI space. 100 masks were summed to create a probabilistic atlas of the central sulcus where voxel intensity is the percentage of participants with central sulcus passing through.

S1-index location was estimated relative to vertex using a mask of meta-analytic mean MNI coordinates for S1-index (MNI[-48,-21,50]), transformed into
scanner/anatomical space per MRI. To account for non-alignment between head and
scanner axes, nasion, inion, and vertex on each image were used to form a plane,
NIV (i.e., mid-sagittal). The nearest voxel to S1-index on the scalp was estimated,
and projected orthogonally onto NIV. This projection was used to generate six pairs of
coordinates (x,y) between S1-index and NIV. Each pair’s Z-coordinate was recorded
as the most superior scalp voxel where x- and y-coordinates matched the projection.
Distances between adjacent points, and the distance between S1-index and vertex
were calculated. For anterior distances, the y-coordinate of the S1-index projection
onto NIV was subtracted from the vertex y-coordinate and divided by the cosine of
the angle between nasion-inion and scanner y-axis.

**Experiment 1: Mapping effects of TMS on tactile discrimination thresholds**
Participants trained to detect and discriminate vibrotactile stimuli (150 Hz, 50 ms,
Oticon bone-conductor) on their right index finger. The first training was 48 trials of 2-
interval forced choice (2IFC) detection, in which a pseudorandom interval contained a
target. 1s intervals were preceded by a 250 ms light emitting diode (LED) flash on the
left (first) or right (second interval). Targets were presented mid-interval, and were
followed by a 2.5 s response period. Participants released a pedal under their left
(indicating the target was in the first) or right foot (second interval). Incorrect
responses were followed by 2x250 ms flashes from both LEDs. Trials were separated
by 1 s. Target intensity began at 0.8 (arbitrary units), adjusted by QUEST (Watson
and Pelli, 1983) implemented in PsychToolBox3 (Brainard, 1997). The second
training was 2IFC intensity discrimination. One interval contained a ‘weak’ (1.5x
detection threshold), the other a ‘strong’ vibration (starting at 1.8x weak intensity).
Participants responded with left feet for strong (targets) in the first, and right for the second interval. Threshold for 2IFC tasks was ~76 % correct, taken as the final trial’s value of QUESTMean. The third training was 1IFC intensity discrimination. Half the intervals contained a weak (1.5x detection threshold), and half a strong vibration (starting at 1.8x weak intensity). Participants classified stimuli as 'strong' (left) or 'weak' (right pedal). The strong intensity was adjusted with QUEST. Threshold was 69 % correct (equivalent to 76 % in 2IFC). A single pulse of TMS at 50 % maximum stimulator output (MSO) was presented ~30 cm away from the participant's head, 25 ms after the onset of each vibration.

We refer to scalp and brain coordinates thus: ORIGIN(lateral, anterior). Right and anterior are positive, left and posterior negative. For example, 5 cm left and 1 cm anterior to vertex: Cz(-5,1); 2 cm posterior to the optimal FDI location: FDI(0,-2). MNI neuroimaging coordinates are: MNI(X,Y,Z), in mm. Resting motor threshold (RMT) for the FDI was estimated using motor evoked potentials (MEPs) in the electromyograph (EMG, AD Instruments Powerlab 16/30; BioAmplifier, silver/silver-chloride electrodes over FDI belly and distal second metacarpal, Criswell, 2011; monophasic Magstim 200^2 BiStim module, standard BiStim mode, figure-of-8, 100 mm outer diameter coil). Test pulses ~5-10 s apart were presented while the coil was moved around, at approximately Cz(-5,1), starting at 50 % MSO, increasing and decreasing to find the threshold (i.e., 5/10 trials with minimum peak-to-peak MEP amplitude of 50 uV, both peaks within 20-60 ms). The coil handle pointed posterolaterally, approximately 45 degrees to the midline; current anterior-to-posterior.
The mapping experiment was 10 blocks of 48 trials of 1IFC intensity discrimination, with TMS at one of 10 pseudorandomly ordered locations (Fig. 1F, white circles). A grid of ten locations was placed on participants' heads, with the origin, location 2, \( L_2 = \text{FDI}(0,0) \). The 9 other locations were: \( L_1 = \text{FDI}(+2,-2) \), \( L_3 = \text{FDI}(0,-2) \), \( L_4 = \text{FDI}(0,-4) \), \( L_5 = \text{FDI}(-2,+2) \), \( L_6 = \text{FDI}(-2,0) \), \( L_7 = \text{FDI}(-2,-2) \), \( L_8 = \text{FDI}(-2,-4) \), \( L_9 = \text{FDI}(-4,0) \), and \( L_{10} = \text{FDI}(-4,-2) \).

Two participants (#3, #8) could not perform training. Two participants (#10, #12) performed poorly with TMS (i.e., floor effects, QUEST reached ceiling) on 8 blocks. #7 showed floor effects on six, #11 on two, and #5, #6, and #9 on one block each. Floor effects reduce variability at lower performance ranges (Holmes, 2009). A scatterplot of participants' across-block means against across-block SDs revealed two outliers (#10, #12), with low coefficient of variation (SD/mean). These participants were removed; the reported mean effects of TMS are therefore likely underestimated.

**Experiment 2: Controlling for non-specific effects of TMS**

Experiment 1 contained one task and 10 locations. Changes in performance across locations could be due to differences in TMS-related discomfort rather than effects on the brain (Meteyard & Holmes, 2018; Holmes & Meteyard 2018; http://tms-smart.info). Experiment 2 improved TMS localization and participant performance. Participants also performed auditory intensity discrimination to control for non-specific TMS effects.
EMG data were recorded from electrodes over FDI and flexor digitorum superficialis (FDS; Criswell, 2011). M1 was systematically mapped at 20 grid locations oriented ~45 degrees to midline (Fig. 1A, white circles). During discrimination, seven TMS locations were stimulated (4x2 grid, 2 cm spacing). An extra location was added, at FDI(-1,-1), as our best guess (at the time) of optimal S1-index location: L1=FDI(0,0), L2=FDI(0,-2), L3=FDI(-1,-1), L4=FDI(-2,0), L5=FDI(-2,-2), L6=FDI(-4,0), and L7=FDI(-4,-2), see Fig. 1C (white circles). Participants performed two counterbalanced 1IFC intensity discrimination tasks (vibrotactile, auditory). In auditory blocks, a speaker was positioned near participants' hands. Target frequency was 200 Hz. Weak intensity was 2x detection threshold, strong was 1.5x discrimination threshold above the weak intensity. 20 trials with fixed intensity were used. Based on unpublished data, TMS was triggered 50 ms after stimulus onset (i.e., approximately mid-way through stimulus processing, assuming ~25ms conduction time). A 75 mm outer diameter TMS coil was used.

Participants' heads were measured. Five pulses of TMS were presented at each of 20 locations on the 5(medial-lateral)x4(anterior-posterior) grid (Figure 1A, white circles), with 1 cm spacing, centered on Cz(-5,1). The mean MEP amplitude across 5 trials at each location was recorded. The 20 locations were tested sequentially, starting anteromedially, #1, Cz(-3,2.5), proceeding posterolaterally to #4, Cz(-3,-0.5), then #5, Cz(-4,2.5), finishing at #20, Cz(-7,-0.5). The location with maximal mean MEP amplitude per participant was designated M1-FDI; RMT was measured here.

Participants performed tactile and auditory tasks in two counterbalanced ~60 minute
sessions. Two training tasks were performed per session: 2IFC detection, 2IFC intensity discrimination. The experiment included seven blocks of 20 trials, each with TMS over one pseudorandomised location. Data were analyzed as proportion correct, d-prime=Z(Hits)-Z(False alarms), and criterion=-0.5*(Z(Hits)+Z(False alarms), Tamè & Holmes, 2016). The coil was held at ~45 degrees to midline, handle posterolaterally, current anterior-to-posterior.

**Scalp measurements of S1-index**

The scalp locations of S1-index across all our available neuronavigated TMS data from nine unpublished experiments were summarised. For all measurements we had a recent structural MRI scan, and used atlas coordinates derived either from individual FMRI data, from group (N=20) FMRI data, or from meta-analysis (Holmes & Tamè, in press). All available sources of information were used. The target was on the anterior bank and/or crown of postcentral gyrus. Anatomical criteria (i.e., over postcentral gyrus, posterior to central sulcus) were prioritised over FMRI data. FMRI coordinates, whether based on individual, group, or meta-analysis, indicated that S1-index was, in every participant, lateral to or on the lateral border of the precentral gyrus ‘hand knob’ (Yoursy et al., 1997).

**Analytic strategy**

This report provides multiple independent estimates of the optimal scalp location to stimulate S1-index. The analysis was largely exploratory, to estimate rather than hypothesis-test. Means and SDs are given for distances, locations, and TMS parameters; means and standard errors (SE) are given for behavioral performance,
muscle responses, and between condition differences, where statistical comparisons
are made. Our experimental question is: are there consistencies in optimal TMS
location across the samples typically used in similar TMS experiments (N≈12).

Reported p-values are uncorrected, unless otherwise stated. We believe minimizing
sample size is important for human brain stimulation experiments, to reduce the risk
that TMS poses - three of our participants have suffered syncope or fainting (Reader
et al., 2017). Our approach is therefore to search for large, consistent effects (Smith
& Little, 2018), and accumulate multiple, independent, converging sources of
evidence. Where statistical tests are used, we are comfortable with the conventional
long-run false positive error rate of 5 % (Lakens et al. 2018). Data, scripts, and
previous versions of our work are freely available at https://osf.io/c8nhj/.

Results and statistical analyses

Functional MRI data. The group peak voxel locations and probabilistic anatomy for
BOLD responses to vibrotactile stimulation of ten digits are in Table 1. The data are
unable to resolve different S1 subregions, so only peak S1 voxels are reported. The
differential contrasts, of each digit against the other four, resulted in lower BOLD Z-
scores (across-digit mean±SD Z=2.69±0.86) than single condition contrasts
(mean±SD Z=4.14±0.65), as expected – the single contrasts do not account for
general task-related or finger non-specific activity common to all conditions in
contrast with rest. The peak voxels in the two contrasts were mean±SD 5.44±4.05
mm apart. Left hemisphere peak voxel locations ranged superiorly from MNI(-40,-
30,64) for the little, to MNI(-50,-18,44) for the index; right hemisphere ranged from
MNI(40,-30,66) for the ring, to MNI(56,-12,46) for the index finger. The peak
differential contrast voxels for S1-index were MNI(-48,-14,50) for left, and MNI(48,-12,54) for right hemisphere.

Probabilistic atlas of the central sulcus, and S1-index scalp location. The 100 central sulcus masks were summed into a single image, indicating the percentage of participants whose central sulcus included each voxel (Fig. 1B, left panel). The brain registration was less variable than the head registration (Fig. 1B, right panel). The between-participant range in Y-axis position of the central sulcus at the level of S1-index, MNI(-48,-21,50), was around 2-3 cm. The mean±SD location of S1-index projected onto the scalp was 6.8±0.4 cm lateral and 0.6±0.7 cm posterior to the vertex (Fig. 1B, 1D, 1E, blue square; Table 2).

Experiment 1: Mapping effects of TMS on tactile discrimination thresholds. In training, nine participants’ mean±SE 2IFC detection threshold was 0.473±0.105 (A.U.); 2IFC discrimination threshold was 1.50±0.09 times weak intensity (1.71±0.26 dB, D’Amour and Harris 2014; Tamè et al. 2014); and 1IFC discrimination threshold was 1.52±0.15 times weak intensity (1.64±0.41 dB). Mean±SD RMT=44.3±4.9 % MSO. TMS was applied at mean±SD=119±1.7 % RMT (mean±SD=52.7±5.3 % MSO). Due to researchers not recording data, scalp locations for M1-FDI were available for only seven participants, with mean±SD Cz(6.0±1.0,0.9±0.6) cm. Overall mean±SE discrimination threshold across 10 locations was 2.73±0.26 dB (Fig. 1F), with best performance (2.3±0.4 dB) at FDI(0,-2), and worst (3.36±0.31 dB) at FDI(-2,2) (Fig. 1D, 1F, black cross). Thresholds were higher (worse) than in training, with locations 5, 6, and 9 significantly (.012≤p≤.032). Pairwise comparisons between all 10 sites.
revealed significant differences between FDI(-2,2), and locations 2, 3, 4, 6, 8, and 10 (.026≤p≤.049). Across locations, mean±SE MEPs were 0.178±0.039 mV, from
0.106±0.027 mV at FDI(0,-4), to 0.439±0.186 mV at FDI(0,0). Within-participant correlations between MEP amplitude and discrimination threshold across 10 locations varied from r(8)=-0.499 to r(8)=.417 (uncorrected two-tailed ps>.14). R-values were converted to Z-scores to allow parametric analysis; across participants, mean±SE Z-score was small (0.100±0.110, t(8)=0.905, p=.389).

**Experiment 2: Controlling for non-specific effects of TMS.** Training performance on 2IFC detection was mean±SE=0.0483±0.0112 (A.U.) for tactile, and 0.0319±0.0029 for auditory stimuli, t(11)=0.145, p=.887. 2IFC intensity discrimination performance was 0.352±0.055 (1.27±0.16 dB) for tactile, and 0.524±0.113 (1.71±0.30 dB) for auditory, t(11)=.876, p=.160. Participants' head sizes were a mean±SD=38.0±2.3 cm from nasion-inion, and 36.5±1.8 cm between pre-auricular points. Across locations, mean±SE MEP amplitude=0.197±0.056 mV, from 0.003±0.002 mV at Cz(-5.4,3.5), to 0.526±0.283 mV at Cz(-6.1,-0.1) (Fig. 1A). Locations 3, 6, 9-11, and 15 produced MEPs significantly greater than zero (.005≤ps.020). Pairwise comparisons revealed no clear pattern of differences. Across participants, Cz(-4.7,-1.5), Cz(-3.9,2.1), Cz(-4.7,1.4), Cz(-5.4,2.1), and Cz(-6.8,0.7) produced maximal MEPs in one participant, Cz(-3.2,1.4) and Cz(-6.1,-0.1) in two, and Cz(-5.4,0.7) in three. Mean±SD optimal location was Cz(-5.0±1.0,0.8±1.0). Mean±SD RMT at this site was 40.4±7.0%MSO.

TMS was presented during the experiment at a mean±SD of 120±0.6% RMT (48.4±8.4% MSO). Performance was worse with tactile (mean±SE d-
prime=1.06±0.12) than auditory targets (1.61±0.2, t(11)=2.78, p=.018). Response
biases (tendency to respond 'stronger') were negligible, and comparable between
touch (mean±SE criterion=-0.005±0.039) and audition (0.055±0.054, t(11)=0.938,
p=.369). Effects of TMS were assessed by differences between auditory and tactile
tasks per location. TMS over FDI(-2,0) resulted in the largest decrement in
performance (tactile mean±SE d"=1.05±0.30 vs. auditory=1.93±0.30, mean±SE
difference=0.880±0.265, t(11)=3.32, p=.007), with FDI(0,0) second largest
(0.942±0.194 vs. 1.73±0.346, difference=0.788±0.318, t(11)=2.48, p=.031, Fig. 1C,
1D black 'target'; Table 2). All other sites showed worse performance for tactile
targets, but none significantly. None of the response biases differed between auditory
and tactile tasks, but participants were more likely to report 'weaker' tactile targets
with TMS over FDI(0,0) (mean±SE criterion=-.136±0.075), than FDI(-2,0)
(0.120±0.087, t(11)=2.39, p=.036), or FDI(-2,-2) (0.130±0.110, t(11)=2.26, p=.045).

MEPs were recorded from FDI and FDS, were monitored during experiments, but
data were saved only for eight participants (#5-12). During the tactile task, mean±SE
MEPs were smallest at FDI(-4,0) (FDI=0.058±0.026 mV) and FDI(-2,-2)
(FDS=0.014±0.010 mV) and largest at FDI(0,0) (FDI=1.51±0.49 mV, FDS= 1.22±0.43
mV). During the auditory task, MEPs were smallest at FDI(-2,-2) (FDI=0.01±0.01 mV;
FDS=0.01±0.01 mV) and largest at FDI(0,0) (FDI=0.79±0.29 mV, FDS= 0.55±0.21
mV). The smallest 'MEPs' (~0.01 mV) were not different from zero, much lower than
the MEP threshold, and likely reflect electrical noise. Comparing auditory and tactile
tasks, MEPs were not significantly different at any location. There were no significant
correlations between performance (d') and MEP amplitude, either for tactile or
auditory tasks alone, the differences between them, for either muscle, or for both
muscles combined (nine comparisons on Z-scores, all t(7)≤1.75, all uncorrected
p≥.125).

Scalp measurements of S1-index. The mean±SD scalp location of S1-index was Cz(-
8.0±0.9,-0.4±1.0) (left hemisphere, Fig. 1D, magenta circle; Table 2), and
Cz(8.4±1.1,-0.4±0.5) (right hemisphere). Combining hemispheres across 15
participants, S1-index was at Cz(±8.1±1.0,-0.3±0.8). For seven participants,
mean±SD S1-index was at FDI(±2.4±1.0,-0.5±1.3).

Discussion

Re-analysis of FMRI data revealed the peak voxel for right index finger was very
close to the meta-analytic mean location of S1-index in BA3b and BA1. The
probabilistic central sulcus atlas revealed a 2-3 cm anterior-posterior range in central
sulcus location at the level of S1-index. This implies that researchers using template
MRI to position TMS coils are likely to make Y-axis errors of several cm in locating
the central sulcus. Projected onto the scalp, S1-index is 7 cm lateral, and 0.5 cm
posterior to vertex. These distances are likely to be slight underestimates, given that
participants typically have hair (not visible on MRI), and a bathing or EEG cap
between scalp and TMS coil. This underestimation is between 0.2 and 1.0 cm (Table
2). In Experiment 1, the location of maximal interference of TMS with tactile intensity
discrimination thresholds was 2 cm lateral, and 2 cm anterior to M1-FDI. Experiment
1, however, is relatively weak: two participants could not complete the task, two were
removed, and the statistical tests did not pass conservative multiple comparison
corrections. Instead, Experiment 2 provides strong evidence that maximal
interference with tactile intensity discrimination is 2 cm lateral to M1-FDI. Experiment
2 allows greater confidence that M1-FDI was optimally localized and that tactile
interference was due to a specific worsening of tactile relative to auditory
discrimination. Conservative correction for multiple comparisons revealed that the
only significant effect of TMS on tactile intensity discrimination was 2 cm lateral to
M1-FDI.

The more anterior location found in Experiment 1 than 2 may be due to the different
tasks used (threshold estimation vs. discrimination); to between-participant
differences in central sulcus anatomy or head shape; to variability in the precision of
our TMS methods and head measurements; or to increased TMS-related discomfort
at the most anterior site in Experiment 1 (Meteyard & Holmes, 2018; Holmes &
Meteyard, 2018). Experiment 2 included a control task so that TMS-related
discomfort was matched, and task-related differences were the dependent variable.
Without independent MRI evidence, the most likely cause is measurement error and
increased TMS-related discomfort at the most anterior site in Experiment 1.

Here, we reported multiple independent lines of evidence (Table 2, Figure 1) which
supports findings from a recent systematic review (Holmes & Tamè, in press): the
optimal location for stimulating the hand area of primary somatosensory cortex, on
average, is ~2 cm lateral, and ~0.5 cm posterior to M1-FDI. This finding of S1-hand
being more lateral than M1-hand is consistent with studies in which both M1-hand
and S1-hand are measured together (e.g., Blatow et al. 2011), and with the work of
Seyal and colleagues (1997), who systematically mapped TMS effects on tactile
detection and discrimination at 25 locations in a grid centered on M1-hand. They
found maximal interference when the TMS coil was 4 cm lateral and 0-2 cm posterior
to M1-hand (Figure 2a and 2b in Seyal et al. 1997).

Assuming previous TMS studies found M1-FDI/APB in a similar location to our data,
these results imply that TMS studies targeting S1-index have been, on average, 2.25
cm away from their target (Table 1). This is not a trivial distance. The mean figure-of-
eight TMS coil used in these studies has a 7.5 cm outer wing diameter, implying an
error of 30% of coil diameter. This is likely to impede stimulation effectiveness. TMS
over motor cortex is sensitive to coil position changes of a few millimeters (e.g.,
Raffin et al., 2015). These large distances between the likely location of S1-index,
and the locations targeted in prior experiments may explain why otherwise well-
designed experiments may fail to interfere significantly with tactile perception (e.g.,
Convento et al. 2018, reviewed by Holmes and Tamè, 2018). Below, we discuss
possible sources of variability in stimulating S1 using TMS.

**Sources of variability in stimulating S1**

Variability in TMS studies arises from participants, experimenters, and procedures.
Participant-associated variability includes head size and shape (Zilles et al. 2002;
Xiao et al. 2018), brain area size, shape, folding, location, and function.
Experimenter-associated variability arises from the selection, measurement, and
registration of anatomical landmarks and reference points (nasion, inion, vertex), and
the positioning and orientation of the coil. Procedure-associated variability includes
the target, timing, intensity, orientation, waveform, frequency, and orientation of TMS.

We were surprised by the large within-participant and between-session/experimenter variability during our studies. This variability may explain the potentially surprising finding of Experiment 1, with maximal thresholds 2 cm lateral and 2 cm anterior to M1-FDI. Measurements on the scalp varied, laterally and anteriorly, by 3-4 cm between participants for M1-FDI relative to vertex (Niskanen et al. 2010), S1-index relative to vertex, and S1-index relative to M1-FDI. In part, this is due to errors in scalp measurement, MRI registration, and locating M1-FDI. In large part, however, it likely reflects between participant anatomical differences. Better training, communication, and day-to-day practice will minimize experimenter error; better understanding of M1-hand and S1-hand are required to optimise TMS protocols. Given the potential sources of variability in stimulating S1, we recommend consistent, systematic, and numerical reporting of every aspect and stage of TMS studies (Rossi et al. 2009; Rossini et al. 1994, 2015; Chipchase et al. 2012). This should be done for all studies, regardless of whether neuronavigation was used.

**Limitations**

Our approach relied on numerous sources of information which, we argued, converged on the result that S1-index is 2 cm lateral to M1-FDI. Despite this convergence, one might question whether meta-analysis of reported FMRI coordinates, or averaging FMRI data across participants is sufficient. We cannot distinguish between Brodmann’s area BA3b, BA1, or BA2 with our FMRI data, as our localizers were not sufficiently powerful. Similar limitations may apply to our TMS
data (Fox et al. 2004). We also cannot account for biases intrinsic to FMRI – the data rely on oxygenation changes rather than neural activity, and may be biased by non-neural structures (Schweisfurth et al., 2014). Further, single peak voxel coordinates derived from multiple studies and participants do not reflect the likely extent of S1 activation following index finger stimulation, nor the total S1 territory involved. Better methods to estimate the optimal scalp location for S1-index TMS may be to combine probabilistic maps of S1 with the likelihood of TMS, accounting for individual brain anatomy (Petrov et al. 2017). The overlap or convolution of these probabilistic maps might provide more accurate estimates of the scalp locations necessary to stimulate S1-index. This approach represents a clear goal for future work, and would be extremely useful for interpreting previous results and planning new studies (Xiao et al., 2018). Generating such a statistic will need to account for TMS coil size, shape, position, and orientation, intensity, waveform, frequency, and pattern; scalp-to-brain distance, cortical folding, and the size and function of the cortical area under study.

We have criticized the standard heuristic based on M1-FDI to locate S1-index, but our methods also rely on TMS over M1-FDI: the origin of our maps was M1-FDI; TMS intensity was set according to M1-FDI threshold. These practices are very common in TMS research, but we must be cautious about the circularity. There may be no reason why S1-index is best localized using M1-FDI as a reference, and no reason why parameters optimal for M1-FDI should be optimal for S1-index. Addressing this circularity is outside the present scope, but is important for future studies.

**Recommendations for locating S1-index in transcranial stimulation studies**
Depending on available equipment and funding, transcranial stimulation studies may need different methods to locate their targets. Ideally, neuronavigation with a recent high-resolution structural MRI and functional localizer will be used for each participant. Systematic review showed that very few studies met this ‘gold standard’ (Holmes & Tamè, in press). If individual FMRI is unavailable, individual MRI with group-level localizers or coordinates may suffice. The FMRI data need to be interpreted in conjunction with anatomical criteria. Registration of the participant's head to the MRI needs to be done carefully; we recommend recording head and scalp measurements systematically - in one participant, we noticed scalp coordinates well outside other participants’; re-registering the MRI revealed that the wrong calibration file had been used, leading to ~3 cm coil positioning error. If a participant’s MRI is unavailable, then standard MRI templates, registered onto the participant’s scalp, provide only an approximate localization. The probabilistic central sulcus atlas we reported (Fig. 1B), suggests registration errors of several centimeters are likely. Without neuronavigation, scalp measurements using the 10:20 or 10:10 systems may be the only, very approximate, localization method. If the location of a target is estimated relative to that of primary motor cortex (i.e., using muscle twitches or motor-evoked potentials), or other functionally-defined locations, then researchers should use as many relevant sources of evidence to justify any heuristics used. Our work suggests that even very-commonly reported heuristics are not optimal for locating the intended target. Such heuristics may not be evidence-based.
Conclusion

More than a century after the first electrical stimulation of human somatosensory cortex (Cushing, 1909), the accuracy of TMS coil positioning remains questionable. The localization error in previous TMS studies of S1-hand is likely about 2.25 cm. Evidence from the independent sources reported here converged on the finding that S1-index is about 7-8 cm lateral to the vertex, or about 2 cm lateral and 0.5 cm posterior to the scalp location for eliciting MEPs in the FDI muscle. These estimates cannot be relied upon for any single participant – the range of scalp locations across participants was 3-4 cm in each direction for each location. Multiple sources of evidence for target location – probabilistic anatomy, group data, scalp measurements, meta-analyses, and the gold standard of individual (F)MRI – should be sought in every TMS study. To improve localization methods, we recommend systematic reporting of participants' head sizes and all locations targeted, both along the scalp and, if available, in MRI scanner/anatomical and standard (e.g., MNI152) coordinates. The results of previous TMS studies targeting the index finger area of S1 need reassessment.
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**Fig. 1: Locating primary somatosensory cortex in human brain stimulation studies.** Evidence for the scalp location of the primary somatosensory cortex representation of the right index finger (S1-index). All coordinates are in centimetres (cm) lateral to (i.e., left of) and anterior to (i.e., forward of) the vertex (Cz), or in MNI space. **A.** Mean motor evoked potential (MEP) amplitude during systematic mapping of the first dorsal interosseus muscle's primary motor cortex representation (M1-FDI) on the scalp in Experiment 2. Red square at Cz(-5.2,0.4): mean location of M1-FDI from all available studies conducted in the laboratory (N=56); white circles: locations tested. **B.** Probabilistic anatomy of the central sulcus, as estimated from 100 MRI scans. Colours on the brain scan represent the proportion of participants with central sulcus at that location. Blue square and green cross-hairs: mean reported MNI coordinate for the location of S1-index across 54 FMRI studies, MNI(-48,-21,50). The graph shows a cross-section along the MNI Y-axis for the selected coordinate. The range of likely central sulcus distances along this axis, after transformation of either the whole head (black), or the brain (grey), is 2-3 cm. **C.** TMS-related interference with tactile intensity discrimination (N=12, Auditory d’ – Tactile d’, t(11)-scores), is highest 7 cm lateral, and 0.76 cm anterior to the vertex. Thin black contour: uncorrected 1-tailed statistical significance (alpha) threshold (p≤.05); thick black contour: alpha threshold Bonferroni corrected for 7 locations (p≤.007); black 'target': maximum tactile interference; red square: M1-FDI; white circles: locations tested. **D.** Summary of all scalp locations (M±SD) studied in this report and those from a recent systematic review. Magenta circle: S1-index based on individual fMRI-guided TMS neuronavigation; yellow triangle: Mean C3 location on 101 participants' heads; open squares: estimated mean scalp location targeted for 43 TMS studies using M1-FDI as
a reference point (black); 16 TMS studies using M1-thenar as a reference point (mid grey); 21 TMS studies using hand movement as a reference point (light grey); black triangle: estimated mean scalp location targeted for 16 TMS studies using C3 as a reference point; black diamond: estimated mean scalp location of M1-FDI according to a meta-analysis. Black cross: mean location of maximum intensity discrimination thresholds in Experiment 1; black 'target': mean location of maximum difference between auditory and tactile intensity discrimination performance in Experiment 2. 

E. fMRI data. Re-analysis of FMRI data from Tamè and Holmes (2016): red-yellow shading shows the contrast between the right index finger versus all other fingers on the right hand. F. Mean tactile intensity discrimination thresholds for 9 participants in Experiment 1. White circles: locations tested. G. Mean±95% confidence ellipsoids for M1-FDI (red) and S1-index (magenta) locations, as used by Tamè and Holmes (2016). H. Scalp landmarks used in the 10:20 electrode positioning system. White circle: vertex; green circles: other scalp landmarks and electrode positions, including C3', often positioned as indicated, at 2 cm posterior to C3, though likely located ~3.6 cm posterior to C3.
**Table 1: Peak BOLD signal changes at the group level, to vibrotactile stimulation of left and right digits in 20 healthy participants**

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<th>MNI x</th>
<th>y</th>
<th>z</th>
<th>Z</th>
<th>Probabilistic anatomy (%)</th>
<th>Central gyrus</th>
<th>Brodmann's area</th>
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<td>57 Post</td>
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<td>3.44</td>
<td>5  Pre</td>
<td>49 Post</td>
<td>2 40 0 15 71 8</td>
</tr>
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</table>

x: MNI x-coordinate in mm; y: MNI y-coordinate in mm; z: MNI z-coordinate in mm; Z: Z-score for the BOLD contrast; Post: postcentral gyrus; Pre: precentral gyrus. Probabilistic anatomy based on the Juelich probabilistic cytoarchitectural atlases viewed in FSL-view.

Data for the index finger are highlighted in bold text.
Table 2: Scalp locations of M1-FDI, S1-index, and C3/C4 relative to vertex (Cz), from seven independent sources of evidence

<table>
<thead>
<tr>
<th>Location and source</th>
<th>Location relative to vertex (Cz) mean±SD cm (min:max)</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
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<td>-5.2±0.8 (7.0:-</td>
<td>-5.2±0.9 (3.5:5.9)</td>
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<td>S1-index, TMS meta-analysis (N=96 studies, 1991-2017)*</td>
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<td>-5.9±0.9 (-8.2:-)</td>
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<td>C3/4, head measurements (2016-18)</td>
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<td>S1-index, FMRI meta-analysis (LH N=425; RH N=316, 54 studies, 1999-2017), projected onto scalp in MRI</td>
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<td>S1-index, FMRI study (N=20, 2012-14), group contrast projected onto scalp in navigated TMS studies (2016-18)</td>
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<td>-7.8±0.9 (-10.0:</td>
<td>-0.2±1.0 (-1.5:1.4)</td>
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</table>

* Collapsed across hemispheres, and using assumed scalp locations for M1-FDI/M1-APB representations where not reported