Involvement of Human Primary Somatosensory Cortex in Vibrotactile Detection Depends on Task Demand

Luigi Tamè[1,2,3] and Nicholas P Holmes[4]

[1]Centre for Integrative Neuroscience & Neurodynamics, School of Psychology & Clinical Language Sciences, University of Reading, Reading, UK

[2]Center for Mind/Brain Sciences, University of Trento, Rovereto, Italy

[3] Department of Psychological Sciences, Birkbeck, University of London, London UK

[4]School of Psychology, University of Nottingham, Nottingham, UK

Address for correspondence:

Luigi Tamè

Department of Psychological Sciences

Birkbeck, University of London

Malet Street, London WC1E 7HX, United Kingdom

E-Mail: luigi.tame@gmail.com

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Abstract

Detecting and discriminating sensory stimuli are fundamental functions of the nervous system. Electrophysiological and lesion studies suggest that macaque primary somatosensory cortex (SI) is critically involved in discriminating between stimuli, but is not required simply for detecting stimuli. By contrast, transcranial magnetic stimulation (TMS) studies in humans have shown near-complete disruption of somatosensory detection when a single pulse of TMS is delivered over SI. To address this discrepancy, we measured the sensitivity and decision criteria of participants detecting vibrotactile stimuli with individually-tailored fMRI-guided TMS over SI, over a control site not activated by vibrotactile stimuli (inferior parietal lobule, IPL), or away from the head (a no TMS condition). In a one-interval detection task, TMS increased participants' likelihood of reporting 'no' target present regardless of site, but TMS over SI also decreased detection sensitivity, and prevented improvement in tactile sensitivity over time. We then measured tactile thresholds in a series of two-interval forced-choice (2IFC) detection and discrimination tasks with lower dependence on response criteria and short-term memory load. We found that thresholds for detecting stimuli were comparable with TMS over SI and IPL, but TMS over SI specifically and significantly impaired frequency discrimination. We conclude that, in accordance with macaque studies, human SI is required for discriminating between tactile stimuli and for maintaining stimulus representations over time, or under high task demand, but may not be required for simple tactile detection.

Significant Statement

Studies on monkeys have suggested that the primary somatosensory cortex is responsible for discriminating between different vibrations on the fingertips, but not just for detecting these vibrations. However, similar studies in humans suggest that the somatosensory cortex *is* required both for detecting and discriminating between tactile stimuli. We used magnetic brain stimulation to interfere with human somatosensory cortex while healthy volunteers detected and discriminated between vibrations applied to their fingertips. We found that the somatosensory cortex is required for keeping vibrotactile stimuli in memory for short periods of time and for comparing two vibrotactile stimuli, but is not required merely for detecting vibrotactile stimulation. This suggests that human primary somatosensory cortex is not always needed for vibrotactile detection.

1. Introduction

The contribution of the primary somatosensory cortex (SI) to the perception of tactile stimuli on the body remains a debated topic. Neurophysiological (Romo et al., 2002) and lesion (LaMotte and Mountcastle, 1979) studies on monkeys, in accordance with brain stimulation reports in humans (Morley et al., 2007), agree on the critical role played by SI in tactile discrimination tasks. However, they disagree on the contribution of SI in simpler tactile tasks such as detection. Neuroimaging studies in humans suggest a broader role of SI. Responses in somatosensory brain areas are well correlated with participants' behavioural performance (Jones et al., 2007), suggesting that human SI is required for detecting the mere presence of tactile stimuli, and for generating a conscious perception of those stimuli. This is further supported by studies reporting that neural activity (Palva et al., 2005) and blood-oxygenation level-dependent (BOLD) responses (Moore et al., 2013) in the somatosensory cortex correlate with conscious tactile perception. By contrast, single unit recording studies in monkeys suggest that neurons in SI are primarily devoted to signalling the physical presence of a stimulus on the skin yet, paradoxically, their activity fails to predict the monkeys' behavioural performance (i.e., hits and false alarms) on judgments of the very same stimulus' presence (Romo and de Lafuente, 2012). Instead, areas higher in the processing hierarchy, such as secondary somatosensory (SII), parietal, and frontal cortices were more highly correlated with monkeys' tactile detection performance (de Lafuente and Romo, 2006, 2005). Moreover, a classic lesion study in monkeys showed that unilateral surgical removal of the parietal cortex permanently impairs contralesional performance and relearning of tactile discrimination between frequencies in the flutter range (24-52 Hz), but not simple tactile detection (LaMotte and Mountcastle, 1979). These animal studies support the idea that SI contributes primarily to discriminative aspects of tactile processing, but how SI contributes to stimulus detection, conscious perception, and perceptual decision-making remains unclear.

Studies using transcranial magnetic stimulation (TMS) in humans suggest that SI is necessary for conscious detection of touch on the fingers. Cohen and colleagues (1991) reported that detection of electrical stimuli on the index finger was attenuated or completely abolished when single pulse (sp) TMS was applied over contralateral sensorimotor cortex between 200 milliseconds (ms) before and 20ms after the tactile stimulus (Cohen et al., 1991). Subsequent studies using spTMS during tactile detection (McKay et al., 2003), localization (Seyal et al., 1997), or discrimination (Morley et al., 2007) tasks have shown similarly disruptive effects of TMS on performance, namely the ability to detect, localize, and discriminate tactile stimuli (Zangaladze et al., 1999; for review, see Song et al., 2011).

Despite the substantial literature from neurophysiological, lesion, neuroimaging, and neurostimulation studies in monkeys and humans, it remains unclear whether, and to what extent, human SI contributes to detection of tactile stimuli. In particular, the role played by SI in tactile detection remains unresolved, despite some apparently clear-cut previous results (Cohen et al., 1991; Jones et al., 2007; McKay et al., 2003; Song et al., 2011), while in monkeys, SI is not as critical as it is for tactile discrimination (LaMotte and Mountcastle, 1979, 1975). The aim of the present work is primarily to resolve this long-outstanding issue. By tactile detection, we mean the ability of observers to report the presence of a tactile stimulus on the skin better than chance. Statistically reliable detection of stimuli may not be the same as explicit conscious awareness of those stimuli (e.g., Libet et al., 1991), and the experimental designs in these kinds of studies can be critical (e.g., Azzopardi and Cowey, 1997). For the purposes of the present work, we focus only on whether observers are able to report the presence of a vibrotactile stimulus better than chance.

To this end, we tested whether TMS over human SI is equally effective at interfering with tactile detection and discrimination in several experimental designs with different task demands. In seven experiments, fMRI-guided single- or dual-pulse TMS was applied over SI or a nearby control site (inferior parietal lobule, IPL), and, in positive control experiments, over the median nerve at the wrist or a nearby peripheral control site (extensor digitorum

communis, EDC). Similar to most previous TMS studies, our first experiment used a one-interval forced choice (1IFC) design (a 'yes'/'no' task), but, different from them, we measured both the perceptual (i.e., d-prime) and decision (i.e., criterion) components of tactile detection. Furthermore, in subsequent experiments, we used a Bayesian adaptive staircase procedure (QUEST), in a two interval forced-choice (2IFC) design (Tamè et al., 2014) to evaluate whether TMS over SI is equally disruptive for participants' performance when using a task with lower dependence on response criteria, and lower memory load. These two different designs (i.e., 1IFC vs. 2IFC) enabled us to test the contribution of SI in tactile detection and discrimination under different task demands.

We predicted that participants' performance will be significantly impaired when TMS is applied over SI relative to the control site IPL, if SI is critical to perform a certain task. By contrast, participants' performance will be comparable with TMS over SI and IPL in tasks in which SI is not required.

2. General Materials and Methods

2.1 Participants

A total of 20 healthy adults participated in seven experiments. All participants reported normal or corrected vision and normal somatosensation and gave their written informed consent prior to participation. The study was carried out according to the principles of the Declaration of Helsinki (as of 2008), and under local institutional approval. Participants were reimbursed for their participation in the studies at a rate of £7.50 per hour. We used ARM, LabMan, and the HandLabToolbox to document and control experiments and analyze data. The associated repositories are or will be freely available at https://github.com/TheHandLaboratory.

2.2 fMRI localiser experiment

Design. Each participant performed one experimental run for each of the ten digits on their hands, tested as part of a larger, ongoing study. Each run consisted of 10x11.5s 'task' blocks, interleaved with 10x12.5s 'rest' blocks, for a total of 280s, including 20s at the start and end for scanner and signal equilibration. Each block included 8 cycles ON (1s) and OFF (0.5s) of vibrotactile stimulation, while the participant was lying in the scanner with no task.

Stimuli. Vibrotactile stimuli (sinusoidal waveforms at ~100Hz) were delivered to each fingertip using a custom-built MR-compatible piezoelectric-ceramic stimulator (with a plastic rod actuator, surface area 19.6mm^2) driven by a custom waveform generator. We used a vibrotactile stimulus at 100Hz for two reasons: First, the MRI compatible stimulation apparatus that we were using worked optimally at this frequency, being in the middle of its sensitivity range, producing a very strong, clearly supra-threshold stimulus. Second, it is a frequency with which we can stimulate a range of mechanoreceptors. Ferrite low-pass filters surrounded the cables entering the magnet. Instructions and a fixation point were presented on video goggles inside the bore. Stimuli were presented using E-Prime software (Psychological Software Tools Inc.). Earplugs and closed-ear headphones reduced noise caused by the scanner and made the stimulators inaudible.

MRI acquisition. MR scans were acquired using a 3T Siemens TIM Trio MRI scanner and a twelve-channel head coil. Functional scans were acquired using T2*-weighted EPI scans with almost whole-brain coverage (37 slices, TR=2000ms, 3×3×3mm, TE=30ms, flip angle=90°, FOV=192×192mm). We also acquired T1-weighted anatomical scans (MPRAGE, 176 slices, TR=2020ms, 1×1×1mm, TE=2.90ms, TI=1100ms, FOV=256×256mm).

MRI analysis. Raw DICOM files were converted to NIfTI format files using dcm2nii in MRICron (http://www.mccauslandcenter.sc.edu/mricro/mricron/install.html). MRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) version 5.0.6, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). For each run, the following were performed: slice timing correction using Fourier-space time-series phase-shifting; motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith,

2002); 3D spatial smoothing using an isotropic Gaussian kernel of 5mm full width at half maximum (FWHM); Global (volumetric) multiplicative mean intensity renormalization; 100s highpass temporal filtering. Time-series statistical analysis was carried out using FILM with local autocorrelation (Woolrich et al., 2001). Registration of each participant's functional T2*-weighted to high resolution T1- weighted scans and subsequently to the MNI52 standard brain template was carried out using FLIRT, with 6 and 12 degree-of freedom linear transforms, respectively (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

For each participant, the time-series data for finger stimulation were modelled with a single condition boxcar block design (11.5s ON, 12.5s OFF) convolved with a canonical (double-gamma) haemodynamic response function. The six motion correction parameters obtained during preprocessing were entered as regressors of no interest. First-level GLM analysis was carried out for each run. Each participant's structural and functional data were used for their own TMS experiment (i.e., no group averaging of data was performed, apart from to produce the functional volume of interest for illustrative purposes only, in Figure 3. These volumes are group averages (n=20) of the stimulation>rest contrast for all fingers on each hand, separately for left and right hands. The group data displayed used a cluster-creation threshold of Z>2.33, with no whole-brain correction. After applying corrections, only contralateral SI and bilateral SII clusters were sufficiently large to meet the statistical criteria for both hands.)

2.3 SI Localisation

Most previous studies using TMS to stimulate SI determined the target location by moving posteriorly from the functionally-defined motor hot-spot from between 0.5cm to as far as 4cm (Seyal et al., 1992; Song et al., 2011) or using approximate coordinates based on the international 10-20 electroencephalography (EEG) system (McKay et al., 2003; Meehan et al., 2008; Morley et al., 2007). A few exceptions to this used MRI coordinates to identify the SI hand region (Hannula et al., 2008, 2005; Meehan et al., 2008). We localized the TMS

site for both the SI and control IPL brain regions using both anatomical (i.e., the postcentral gyrus or the IPL respectively) and functional criteria (i.e., a vibrotactile activation cluster, or the absence of activation respectively) from fMRI localizer scans, separately for each participant. This procedure allowed greater confidence than all previous reports that the functionally-defined SI hand area was stimulated in each participant. For the left hemisphere the mean±SD distance of participants' coordinates (x,y,z) of the SI site was 11.4±7.89mm lateral, 7.00±5.32mm posterior, and 11.1±6.91mm inferior (Euclidean distance=19.3±7.68mm) to the functionally-defined motor hotspot, as measured on participants' MRI scans in scanner anatomical space. For the right hemisphere the mean distances were 14.2±5.15mm lateral, 7.64±6.30mm posterior, and 15.0±7.46mm inferior (Euclidean distance=23.4±7.18mm). The location of SI in the two hemispheres, relative to the coordinate system origin, was different, compatible with the results of previous fMRI studies that identified SI using unilateral median nerve stimulation (Nihashi et al., 2005) or vibrotactile mechanical stimulation at the fingers (Tamè et al., 2012).

2.4 TMS experiments

Design. Half (5 or 6) of the participants in each experiment were tested with their left hand as the target and right hemisphere TMS, the remainder with their right hand and left hemisphere TMS. We had no hypotheses relating to handedness or about any potential hemispheric asymmetry. All tests were performed in sets of three counterbalanced conditions: A) TMS over the experimental site (SI/median nerve (MN)); B) No TMS (active coil held ~30cm away from the head); and C) TMS over a nearby control site (IPL/EDC). We paid particular care to select active control sites (IPL/EDC), which were as close as possible to, and just as distracting and annoying as the experimental sites (SI/MN). The no TMS condition always occurred between the two TMS blocks, to provide participants a break. For most experiments, 2 sets of 3 conditions were run, with the second set in reverse order (A-B-C-C-B-A or C-B-A-A-B-C). TMS was always present and identical in both intervals of all the

2-interval tasks. The interval containing the target was randomized. A summary of the different experiments is presented in Table 1.

Apparatus & stimuli. In Experiments 2, 3, and 4, Electromyographic (EMG) activity was recorded using Ag-AgCl surface electrodes placed over the first dorsal interosseus (FDI) muscle of the hand contralateral to the hemisphere stimulated. The EMG signal was sampled, digitised, and stored by the BrainSight software for off-line data analysis.

TMS was presented with a Mag&More PowerMag Research 100 stimulator via a 10cm diameter, flat, figure-of-8 shaped coil. BrainSight 2.2.6 (Rogue Research Inc., Montreal, QC) frameless stereotaxy was used for neuronavigation. Vibrotactile stimuli were delivered with bone conducting vibrators (Oticon, Xiamen, BC461-1 polarized), driven by a standard computer's audio card (Vinyl AC'97 Audio wave). Vibrotactile stimulation consisted of sinusoidal waves (200Hz, 50ms, linear rise and fall of 5ms). We used 200Hz for the vibrotactile stimulation because this is an ideal frequency to induce responses from the Pacinian corpuscle, which has the highest vibration sensitivity and lowest thresholds. Tactile stimulators gently pressed on the finger(s). Levers, cords, and pulleys ensured constant pressure, despite finger movement.

Two light-emitting diodes (LEDs) were placed in front of the participant to indicate the stimulation intervals and to provide feedback. Two response pedals were positioned one under each of the participants' feet. Stimulus presentation and response collection were controlled by custom scripts written using MATLAB (Mathworks, Natick) and PsychToolBox 3 libraries (Brainard, 1997). White noise was presented over two loudspeakers positioned in front of the participant to mask any sounds made by the tactile stimulators.

TMS & neuronavigation. Anatomical and functional images from the localizer scans were imported into BrainSight 2.2.6. The first level contrasts for the relevant target finger (index or middle) were used to select TMS target locations. Anatomical (post-central gyrus) and functional (statistical parameter maps) criteria were used together to select target locations. The group mean stimulated locations across participants (total N=20) are

presented in Figure 3.

For each participant, we first obtained the approximate resting motor threshold (RMT) from biphasic stimulation over M1 (by finding the minimum stimulator intensity that produced motor evoked potentials of 50μV or higher on 5 or more out of 10 trials with the hand relaxed (Rossini et al., 1994) (Experiment 2, RMT: mean±SD=44.2±5.69% of maximum stimulator output; Experiments 1 & 3, RMT: 43.8±5.41%; Experiment 4, RMT: 41.1±5.04%). We then determined the optimal coil positions and orientations for experimental (SI), and control (IPL) stimulation. We aimed to minimize motor evoked potentials in the target hand, and twitches in the facial and scalp muscles. In particular, the best position was found to be with the coil handle oriented at approximately 90 degrees, with the handle pointing inferiorly. Coil location was maintained precisely online on every trial using BrainSight neuronavigation software. We typically achieved a localisation error of <0.5mm on every trial (distance from the target spot on BrainSight). When the coil was re-positioned (due to fatigue or on the participant's request), the experiment was stopped and only recommenced when the coil was correctly positioned. On average, the SI site was approximately 13mm lateral, 13mm inferior, and 7mm posterior to the M1 hot-spot (Table 2). The mean locations for the left and right hemispheres for the index and middle fingers are reported in Table S4 of the supplementary material. For stimulation over M1, the coil handle pointed posteriorly and laterally at an angle of about 45° to the sagittal plane. For SI and IPL, similar orientations were initially tried, then coil orientation was adjusted to achieve minimum distance to the target, and minimum side-effects (scalp, neck, and hand muscle contractions, and localised scalp discomfort). It is most likely that our TMS protocol stimulated areas 3b and 1 of SI (experimental site) the most, because of the anatomical position of the gyrus of this subarea in the brain. However, it is not possible for us to say whether areas 2 and 5 were also stimulated. Further, the biphasic TMS pulses would have stimulated different sets of interneurons in this region with each phase of stimulation (Hamada et al., 2013). For the experiments, TMS intensity was set at 120% of RMT. If this intensity caused too much facial discomfort and/or muscle twitches, it

was reduced to a minimum of 110% (i.e., for three participants in one of the experiments).

General procedure. The behavioural methods were very similar to those of Tamè and colleagues (2014). Briefly, participants performed about 20 practice trials starting from the maximum possible intensity of the tactile stimulus. The starting intensity for experimental blocks was set for all participants at 0.5, half of the maximum possible intensity of the Personal Computer's (PC) audio output. Stimulus amplitude was adjusted on each trial in accordance with the QUEST algorithm (Watson and Pelli, 1983). The suggested default settings of QUEST in PsychToolBox3 were used (beta=3.5, percent correct at threshold=82%). Participants kept their eyes open, could see their hands, and were instructed to fixate between two LEDs (Harrar and Harris, 2009), and to keep two foot-pedals pressed, unless indicating their response to a target stimulus. Response accuracy was emphasized, whereas speed was not. Following correct responses, the LEDs were extinguished until the start of the next trial. Following an incorrect response, the LEDs flashed twice briefly before the trial ended in all Experiments except for Experiment 1, in which no feedback was provided. Participants were offered short breaks and water between blocks. Two experimenters remained in the room throughout the session to hold and position the coil, monitor participant safety, and ensure compliance with the instructions.

The number of trials used to calculate threshold was the same for all participants and sessions. In Experiments 2 and 5, each of two blocks per TMS site had 48 trials with two intervals, each with one TMS pulse (96 pulses). In Experiments 3, 4, 6, and 7, it was the same, but with 2 TMS pulses per interval (192 pulses). Each experiment/session last approximately 1 hour. While we did not explicitly control for baseline sensitivity between sessions or days, counterbalancing ensures that differences between TMS over SI and IPL cannot be systematically affected by between-session differences; all our critical comparisons are within-session.

2.5 Analysis

Behaviour. The detection threshold values for experimental and control TMS conditions were converted to decibels (dB) relative to the **no** TMS condition using the following formula: $dB=10*\log_{10}$(TMS threshold/no TMS threshold) (D'Amour and Harris, 2014; Tamè et al., 2014). The discrimination threshold values were obtained by subtracting the no TMS condition from the experimental and TMS control conditions. Hypothesis driven one-tailed t-tests were used for all planned comparisons, with the prediction that TMS over the target site (SI) should impair performance relative to the control site (IPL). The raw data for Experiments 2-7 including the no TMS, SI, and IPL conditions are reported in Table S2, whereas the statistical comparisons between the conditions are reported in Table S3 of the Supplementary Materials.

MEPs. The peak-to-peak MEP amplitude was determined automatically by finding the minimum and maximum values within a search window, starting from 15 ms and ending ~60 ms after TMS, while excluding TMS-related artefacts. All of the experimental programs, the raw data, and analysis scripts are or will be available on the laboratory's webpages (http://neurobiography.info).

3. Experiment 1: TMS over SI impairs vibrotactile detection and prevents improvement over time

In Experiment 1, similarly to previous studies (Cohen et al., 1991; McKay et al., 2003; Seyal et al., 1997), we tested the contribution of the primary somatosensory cortex in a single interval tactile detection task. We examined both tactile sensitivity and the decision criteria adopted by participants when a dual pulse of fMRI-guided TMS was applied at 120% of resting motor threshold (RMT) over SI, 25ms and 75ms after the onset of a 200Hz, 50ms target stimulus (i.e., TMS was applied at the expected onset and offset of the afferent train in SI; Bensmaia et al., 2008; see also Seyal et al., 1992, who suggested 20-30ms as the optimal time for stimulation). We adopted a single interval 'yes'/'no' design (i.e., 1IFC) in which participants had to report whether, in a single temporal interval, a near-threshold

stimulus was present or absent. The target stimulus was randomly present 50% of the time. As in previous reports, no feedback about accuracy was provided. Participants' performance was measured in accordance with signal detection theory to distinguish changes in tactile sensitivity (d') and decision criterion (C, Green and Swets, 1966; Macmillan and Creelman, 1991), well-established measures of sensory perception (see, especially in the present context, Azzopardi and Cowey, 1997).

3.1 Participants

Eleven participants (mean±SD age=28.4±6.24 years, 7 females) took part in the study. Nine were right-handed by self-report, two were left-handed.

3.2 Methods

Vibrotactile detection task, 1IFC ('yes'/'no') design. Participants were instructed to indicate whether the target finger (i.e., index or middle, counterbalanced between participants) was stimulated on each trial. Participants raised their left foot to report 'no' (target absence), and their right to report 'yes' (target presence). There was only one temporal interval and the target was present on half of the trials. No feedback about accuracy was provided (Tamè et al., 2014). Pulses of TMS were applied at 25 and 75ms after stimulus onset. Each trial started with the left LED flashing for 250ms indicating the potential occurrence, after 500ms, of the tactile stimulation. All participants in this experiment had just taken part in Experiment 3. We used the mean threshold obtained in the last 3 blocks of Experiment 3 (i.e., the mean across no TMS, TMS over SI, and TMS over IPL) as the target intensity for Experiment 1. We are reporting the order of experiments non-chronologically for narrative clarity.

3.3 Results

The results of Experiment 1 showed that participants' sensitivity (d') was reduced

when TMS was applied over SI (M±SE d'=1.59±0.285) compared to over IPL (M±SE d'=2.27±0.306; t(10)=2.96, *p*=.007), and compared to no TMS (M±SE d'=2.34±0.323; t(10)=2.45, *p*=.028). When TMS was applied over IPL, sensitivity was comparable to no TMS (t(10)=0.406, *p*=.69). Moreover, participants' decision criteria were also significantly increased when TMS was applied over SI (M±SE C=0.343±0.154, t(10)=-2.57, *p*=.024) or over IPL (M±SE C=0.460±0.168, *t(10)*=-2.65, *p*=.028) as compared to no TMS (M±SE C=0.0872±0.165). The numbers of hits and false alarms used to calculate d-prime and criterion values of each participant are reported in Supplementary Materials (Table S1).

Following previous reports on the role of SI in tactile working memory (Harris et al., 2002, 2001), and to explore the possibility that the effects of TMS over SI may build up over time, we also analyzed the first half (i.e., first 30 trials) and second half (i.e., second 30 trials) of the data separately. Results of the *first half* showed no differences in the participants' sensitivity (d') when TMS was applied over SI (M±SE d'=1.84±0.384) compared either to TMS over IPL (M±SE d'=2.29±0.384; t(10)=1.10, p=.150), or to no TMS (M±SE d'=1.97±0.454; t(10)=0.257, p=.401), and sensitivity when TMS was applied over IPL was not different to no TMS (t(10)=-1.23, p=.124). Conversely, in the *second half* of the trials, participants' sensitivity (d') was significantly lower with TMS over SI (M±SE d'=1.62±0.321) compared to both IPL (M±SE d'=2.60±0.315; t(10)=3.72, *p*=.002), and no TMS (M±SE d'=3.17±0.236; t(10)=4.40, p=.0005). On further exploration, these effects seemed to build up over time for sensitivity (Figure 4A), but stay relatively constant for criterion (Figure 4B). In the second half of the trials, sensitivity when TMS was applied over IPL was not different to no TMS (t(10)=1.41, *p*=.092).

3.4 Discussion

These results concerning participants' sensitivity are compatible with previous reports on humans in which TMS applied over sensory-motor cortex (specifically, 0-4cm posterior to the motor 'hotspot') impaired tactile detection (Cohen et al., 1991). Moreover, differently from

previous reports, we also found a significant difference in the participants' decision criteria, namely a more conservative criterion when TMS was delivered over both SI and IPL compared to no TMS. With TMS, participants were more likely to report that the stimulus was absent, even if their ability to detect that stimulus was unaffected (compare IPL with no TMS). Overall, the results of our first experiment showed that individual fMRI-guided TMS over SI interferes with tactile detection at the fingers, seems to prevent improvement in performance over time (Figure 4A), and that TMS over both SI and IPL affects participants' decision criteria, increasing their reports of 'no stimulus present' (Figure 4B), independently of changes in sensitivity.

4. Experiments 2 & 3: No effect of TMS on 2IFC vibrotactile detection thresholds

Experiment 1 showed that TMS over SI interfered with vibrotactile detection, preventing improvements in performance over time, as if, speculatively, participants were less able to learn the target stimulus, hold it in memory, or build up an internal standard (Harris et al., 2002; Libet et al., 1991; Morgan et al., 2000). Moreover, the mere presence of TMS, regardless of stimulation site, made participants more conservative in their detection responses. In Experiment 2, we reduced the roles of memory load by presenting the critical comparison stimuli within a temporal window of less than 1 second, and we removed (i.e., made ineffective with respect to the purpose of our study, Yeshurun et al., 2008) the effects of response criteria by using a less criterion-dependent two-interval forced choice (2IFC) design. In each temporal interval, to keep the total number of TMS pulses per condition the same, we applied a single pulse of TMS over SI, IPL, or away from the head (no TMS), 25ms after each stimulus onset. Furthermore, in a subsequent Experiment 3 we again applied two pulses of TMS per interval, at 25ms and 75ms after stimulus onset, in place of the single pulse, to potentially increase the TMS interference. We used an adaptive staircase algorithm (QUEST) to determine detection thresholds for the target stimuli (Tamè et al., 2014).

4.1 Participants

Twelve participants (mean±SD age=30.3±10.4 years, 9 females) took part in Experiment 2 and twelve took part (mean±SD age=29.4±6.8**2** years, 8 females) in Experiment 3. Eleven were right-handed by self-report, one was left-handed.

4.2 Methods

Vibrotactile detection task, 2IFC design (Experiments 2 & 3). Participants were informed that they had to perform a two-interval forced choice task to indicate in which of two temporal intervals the target finger had been stimulated. Tactile stimulation was always present in only one interval (i.e., first or second). Each trial started with the left LED flashing for 250ms indicating the potential occurrence, after 500ms, of the *first* tactile stimulation (1st interval). 500ms after the end of the first stimulation the right LED flashed (250ms), indicating the potential occurrence, after 500ms, of the *second* tactile stimulation (2nd interval). 500ms after the second interval, both LEDs switched on until the participant gave their response. In Experiment 2, a single pulse of TMS was applied 25ms after target onset (i.e., 25ms after the time at which the tactile stimulus was or would have been presented, since in one of the intervals there was no target). Experiment 3 was the same as Experiment 2, with the exception that TMS was applied with two pulses per interval, one at 25 and one at 75ms after target onset.

4.3 Results

Unlike many previous TMS reports of interference with detection of supra-threshold tactile stimulation in a 1IFC design, our results showed that single-pulse TMS over SI had no effect on vibrotactile detection thresholds in a 2IFC design. In particular, in Experiment 2 detection thresholds relative to no TMS were not different when TMS was applied over SI (M±SE=0.152±0.571dB) or IPL (M±SE=0.161±0.455dB; SI vs. IPL, t(11)=0.0166, p=.494;

Figure 5A). Moreover, in Experiment 3 we applied two pulses of TMS, at 25ms and 75ms after stimulus onset, in place of the single pulse. The results of Experiment 3 showed a general and significant increase of detection thresholds relative to no TMS both for the experimental (SI, M±SE=2.30±0.848dB, t(11)=-2.72, p=.0100), and control sites (IPL, M±SE=2.42±0.635dB, t(11)=-3.81, p=.001), but again detection thresholds were not significantly greater for TMS over SI than over IPL (t(11)=-0.357, p=.377; Figure 5B).

4.4 Discussion

These two negative results are very surprising, considering both the results of Experiment 1, and substantial published evidence showing the disruptive effect of single pulse TMS in simple tactile detection tasks (reported effect sizes for comparable experimental conditions range, for example, from d=0.356 in Seyal et al., 1997; to d=5.22 in Hannula et al., 2005, and the infinite effect size corresponding to total blocking of sensation in Cohen et al., 1991). Our sample size of 12 gave us 80% power to detect effect sizes of d>0.76. Almost all previous studies of the effects of TMS on somatosensory perception had sample sizes smaller than 12. The lack of an effect might be explained by the single pulse TMS being too weak or short-lived to interfere with tactile processing in SI in this task (although see Cohen et al., 1991; Seyal et al., 1992 for evidence to the contrary). The results of our Experiment 3 show that, while dual pulse TMS produced a general interference effect by elevating 2IFC tactile detection thresholds, this was not specific to SI as might have been expected from previous reports (Cohen et al., 1991; Seyal et al., 1997, 1992).

To further investigate whether the lack of difference between SI and IPL in tactile thresholds for Experiments 2 and 3 was statistically reliable, we calculated Bayes' factor (BF) for these two experiments. BF is a likelihood ratio of the data supporting the theory to the data supporting the null hypothesis. Conventionally, a BF greater than 3 provides substantial evidence for the theory over the null hypothesis, whereas a BF lower than 0.333 provides substantial evidence for the null hypothesis over the theory (Dienes, 2014). The BF

was 0.301 for Experiment 2 and 0.139 for Experiment 3. Therefore, for both Experiments 2 and 3, we found substantial evidence in support of no difference between the two conditions (i.e., TMS over SI and over IPL). Finally, in both Experiments 2 and 3 we can rule out the possibility that the lack of a difference was due to the ineffectiveness of our TMS protocol because of the significantly non-zero MEPs that we recorded from the hand contralateral to the TMS sites – TMS was strong enough to excite M1, resulting in MEPs recorded from the contralateral hand (see Supplementary Materials).

5. Experiment 4. TMS over SI impairs 2IFC frequency discrimination

In Experiment 4, we tested whether tactile 2IFC frequency discrimination thresholds are susceptible to dual pulse TMS delivered, as in the previous experiments, 25ms and 75ms after stimulus onset, over SI. We expected an interference effect of TMS over SI on the basis of similar previous reports in both monkeys (LaMotte and Mountcastle, 1979) and humans (Knecht et al., 2003; Morley et al., 2007). This experiment served as a positive control for the general effectiveness of our TMS protocols.

5.1 Participants

Twelve participants (mean±SD age=27.7±6.04 years, 9 females) took part in the study. Eleven were right-handed by self-report, one was left-handed.

5.2 Methods

Vibrotactile discrimination task, 2IFC design. Participants were instructed to indicate whether the tactile stimulation in the second interval on the middle finger (i.e., the target, comparison stimulus) was lower (raise left foot) or higher (raise right foot) in frequency than that in the first interval (i.e., the standard) on the index finger. The standard was a vibrotactile stimulus delivered always at 200Hz. TMS was applied at 25 and 75ms after stimulus onset.

5.3 Results

As expected, dual pulse TMS over SI increased frequency discrimination thresholds (M±SE=82.0±6.73Hz) relative both to the no TMS control (M±SE=63.5±6.39Hz, t(11)=-3.26, p=.004), as well as to the full TMS control condition (IPL: M±SE=72.3±7.17Hz, t(11)=-2.11, p=.0291). Discrimination thresholds did not differ significantly between no TMS and TMS over IPL, t(11)=-1.57, p=.0727.

5.4 Discussion

In contrast to the simple detection thresholds investigated in Experiments 2 and 3, using the same pool of participants and near-identical stimuli and methods, TMS specifically and significantly increased discrimination thresholds when applied over SI relative to over IPL (Figure 5C). Although we manipulated target frequency, changes in frequency can be accompanied by changes in perceived intensity, so participants may have used either cue to perform the task. Nevertheless, our data clearly support the hypothesis of a contribution of SI in tactile frequency and/or intensity discrimination, in agreement with previous monkey (de Lafuente and Romo, 2005; LaMotte and Mountcastle, 1979) and human studies (Knecht et al., 2003; Morley et al., 2007; Porro et al., 2007).

6. Experiments 5, 6, & 7: Magnetic stimulation over the somatosensory periphery impairs both detection and discrimination

In the final three experiments, we assessed the effectiveness of magnetic stimulation in modulating both simple tactile detection (Experiments 5 and 6) and discrimination (Experiment 7) thresholds when applied at an even earlier stage of somatosensory processing than SI, over the peripheral nerves (Olney et al., 1990). Indeed, the lack of interference effects in Experiments 2 and 3 may have been either because our particular TMS protocol was not able to impair tactile detection at all, or that 2IFC tactile detection

cannot easily be interfered with by TMS over SI. Experiments 5-7 provide further positive controls for the general effectiveness of our TMS protocols, and followed the same design as Experiments 2-4.

6.1 Participants

The same twelve participants (mean±SD age=27.4±6.11 years, 6 females) took part in Experiments 5, 6 and 7. Eleven were right-handed by self-report, one was left-handed.

6.2 Methods

In Experiments 5, 6 and 7, the pulses of TMS (TMS intensity M±SE=28.7±1.24% of maximum stimulator output), at 0 and 50ms after stimulus onset, were applied over the median nerve at the wrist (experimental site), or over the EDC of the proximal forearm (control site), or with no TMS (the active coil held ~30 cm from forearm). The coil handle was oriented proximally along the forearm. The same 2IFC design for the detection and discrimination tasks were used as for the previous Experiments 2-4.

6.3 Results

Single pulse TMS over the MN (Experiment 5, Figure 5D) increased detection thresholds (M±SE=4.51±1.10dB) relative to TMS over the EDC (M±SE=2.43±0.784dB; t(11)=3.06, p=.008) and no TMS (t(11)=4.08, p=.001). In Experiment 6 (Figure 5E), dual-pulse TMS applied over the MN (M±SE=6.27±1.23dB) increased detection thresholds compared to TMS over the EDC (M±SE=3.23±0.761dB; t(11)=2.93, p=.009) and no TMS (t(11)=5.10, p=.0002). Finally, dual-pulse TMS also increased frequency discrimination thresholds when applied over the MN (M±SE=71.0±11.9Hz) compared to over the EDC (M±SE=40.1±11.1Hz; t(11)=2.62, p=.0155, Experiment 7, Figure 5F) and no TMS (t(11)=5.97, p=.0001). These results argue against the possibility that the lack of effects of TMS in Experiments 2 and 3 was due to the general ineffectiveness of our TMS protocol in

interfering with tactile thresholds at the fingers in a 2IFC detection task.

6.4 Discussion

Experiments 5, 6, and 7 replicated Experiments 2, 3, and 4, with the exception that stimulation was applied 25ms earlier, and over the MN at the wrist (in place of SI), and over the EDC muscles of the forearm (control site, in place of IPL). The results showed that both single- and dual-pulse TMS over the MN increased detection and discrimination thresholds compared to the muscle control site (EDC).

7. General Discussion

We investigated the contribution of human SI to tactile detection and discrimination using individually-tailored fMRI-guided TMS, in both 1IFC ('yes'/'no') and 2IFC designs (Tamè et al., 2014). Our results showed that both the perceptual and decisional components of tactile detection are affected by TMS. When applied over SI, TMS seems to interfere with the maintenance of a representation of the tactile stimulus over time (Libet et al., 1991; Morgan et al., 2000; Recanzone et al., 1992a, 1992b; Wolpert et al., 1998). This 1IFC approach is known to have a greater memory component with respect to the 2IFC design (Harris et al., 2006). Conversely, when tactile detection was tested in the 2IFC design, a task with a lower memory load, and which is more sensitive to sensory inputs (Harris et al., 2006) as well as other task demands, participants' performance was not modulated selectively by TMS over SI. In addition, the reported criterion shift demonstrates that TMS can also bias participants' decision about the presence of a tactile stimulus on the fingers, an issue that, as far as we know, has not previously been noted or addressed in the tactile literature (for a similar report in the visual domain, see Lloyd et al., 2013). The TMS effect on the criterion we observed both for stimulation over SI and IPL may be caused by faint sensations produced by the TMS, inducing participants to increase their criterion to become more conservative and mask them out. More specific investigation is needed to better understand

this effect. Indeed, we believe that increases in response criterion have strong implications for the interpretation of many previous reports of TMS interference with tactile perception. Most importantly, criterion shifts should be taken into account in the design and data analyses of all relevant future TMS studies.

Previous reports that investigated the role of SI in tactile detection arrived at different conclusions. Electrophysiological and lesion studies in the macaque brain suggested that SI (indeed, the whole contralateral parietal cortex) is not required for simple detection of tactile stimuli (LaMotte and Mountcastle, 1979, 1975), whereas studies in humans using single-pulse TMS over sensorimotor cortex showed near-complete disruption of detection (Cohen et al., 1991). The present work suggests a resolution to this discrepancy (see also a similar argument in the blindsight literature, Azzopardi & Cowey, 1997), and reconciles monkey and human studies of the role of SI, by showing that SI is differentially involved in tactile detection as a function of task demand. We speculate that SI is not passively involved in simple detection of incoming inputs, but rather is actively involved in the formation and maintenance of representations of the tactile signal (for example it's frequency and/or intensity) over time (Harris et al., 2002; Katus et al., 2014; Libet et al., 1991; Morgan et al., 2000).

Perception of tactile stimuli occurs following different forms of processing and involving different sensory brain areas to different degrees, depending on the task demands (e.g., Pritchett et al., 2012; Romo et al., 2012; for a review see Tamè et al., in press). In our view, the simplest possible task involves tactile detection in a 2IFC design, where the target stimulus is presented in every trial, in only one of the two intervals (e.g., Tamè et al., 2014). In this task, the participant has a reminder on every trial about how the stimulus feels, and needs only to compare the quality of the two intervals. A slightly more complicated task is tactile detection of a stimulus in a 1IFC design, in which the stimulus is not always present (e.g., Tamè et al., 2011). In this case, many trials can pass until the stimulus is physically presented. This requires the participant to maintain a representation of how the stimulus

feels, and on each trial, to compare the potential stimulus with this memory or 'internal standard' (Libet et al., 1991; Morgan et al., 2000). Furthermore, an internal criterion must be set and used to decide whether there was or wasn't a stimulus (Azzopardi and Cowey, 1997). Other forms of tasks include tactile localization (e.g., Braun et al., 2005) and discrimination, which require the participant to report which stimulus was presented, instead of noticing only whether or when it occurred. Such tactile discrimination tasks may entail more complex processing as compared to simple detection tasks. This last paradigm is typically used to investigate tactile learning (e.g., Harris et al., 2001; Sathian and Zangaladze, 1997). In sum, the specific task that participants perform may determine the amount of resources necessary to complete it and the recruitment of specific brain regions (for a discussion on the difference between tactile detection and discrimination see Romo et al., 2012). In the following, we examine the demands of 1IFC and 2IFC tasks in more detail.

7.1 Tactile detection in a 1IFC design

Most studies in humans similar to the present one have shown that detection of tactile stimuli on the fingers is impaired when TMS is applied in close temporal proximity with the target over contralateral sensorimotor cortex. Cohen and colleagues (1991) found that detection of electrical stimuli on the index finger was attenuated when spTMS was applied 200ms before stimulus onset, and blocked it completely when spTMS was delivered simultaneously to and 20ms after it (Cohen et al., 1991). Similarly, McKay and colleagues (2003) applied trains of electro-cutaneous ulnar nerve stimuli, and reported that when TMS was delivered over the contralateral sensorimotor cortex 100ms before or 20ms after stimulus onset, perception was strongly suppressed (McKay et al., 2003). Our findings are compatible with these results in showing attenuation in participants' tactile detection sensitivity when TMS was applied over SI (Seyal et al., 1997, 1992), confirming that our paradigm successfully replicated this TMS interference effect. However, some previous studies have shown no effects of single pulse TMS over SI (Hannula et al., 2005; Koch et al.,

2006). As suggested by Koch and colleagues (2006), their lack of effect may be because they applied TMS over the somatosensory cortex (Koch et al., 2006) rather than over the combined sensorimotor cortex (Cohen et al., 1991; Pascual-Leone et al., 1994; Seyal et al., 1992). Indeed, concurrent stimulation of sensory and motor cortices may have evoked responses in finger muscles that in turn influenced perception (Koch et al., 2006). Here, we targeted SI using individually-tailored fMRI-guided neuronavigation, and by recording EMG responses, showed a dissociation in motor responses and sensory thresholds (Supplementary Materials, Figures S1**-S2**).

Our findings extend previous results by showing that the reduction in participants' sensitivity with TMS over SI relative to over IPL and no TMS was not constant, but built up over time, perhaps due to a learning effect (Seitz and Dinse, 2007). Indeed, as shown in Figure 3A, participants' performance significantly improved across trials when TMS is not applied over SI, as if the participants are still learning trial-by-trial how to detect the stimulus, and improving their performance. Repeated presentation of the target stimulus allows participants to extract more and more information about it. Yet, with TMS over SI, this learning effect was not seen. This further supports our argument that SI may be extracting and maintaining information about tactile stimuli over trials, rather than merely passively responding to them. When TMS was applied over SI there was no improvement in participants' performance over time, unlike the behavioural improvement seen with no TMS or TMS over IPL. This is compatible with a previous report (Knecht et al., 2003) in which tactile frequency discrimination performance increased across blocks of trials with sham or no TMS. The effect of TMS on this short-term tactile 'learning' effect contrasts with previous accounts suggesting that single pulse TMS can 'block' or 'suppress' the perception of each individual tactile stimulus (Cohen et al., 1991; Hannula et al., 2005; McKay et al., 2003). Rather, we interpret these data as showing that TMS interferes with the formation and maintenance of an internal representation of the tactile stimulus over time (Harris et al., 2002; Morgan et al., 2000), and that the 'pure' perception of tactile stimuli was relatively

unaffected by TMS over SI.

7.2 Tactile detection in a 2IFC design

In Experiments 2-3, we used a 2IFC task known to be less criterion dependent and with lower, and minimal memory demand (Harris et al., 2006; Lloyd et al., 2013). Differently from Experiment 1, this showed that TMS over SI versus IPL did not affect participants' detection performance either when single (Figure 5A) or double (Figure 5B) TMS pulses were applied. This suggests that TMS over SI is not effective in interfering with simple tactile detection when the task is less criterion-dependent and/or requires lower memory load (Harris et al., 2006). In agreement with neurophysiological studies on monkeys (LaMotte and Mountcastle, 1979), SI, under certain circumstances, may not be necessary for detecting a tactile stimulus on the fingers. The fact that the effect of TMS over SI on tactile detection depends on the task (1IFC vs. 2IFC), suggests that SI plays a different role than the simple detection of stimuli (see also (Harris et al., 2006, 2004; Vroomen and Stekelenburg, 2014). Another difference between our first and second experiments was the number of TMS pulses, but we ruled out this potential explanation in Experiment 3, in which doubling the number of TMS pulses still did not impair 2IFC tactile detection for SI relative to the control site.

7.3 Role of the primary somatosensory cortex in tactile detection

We provided evidence that human SI is critically involved in tactile detection only when a certain task (1IFC) with relatively high demands is required. Specifically, we propose that SI is necessary to build up and maintain representations of tactile stimuli (e.g., stimulus frequency or intensity) across time in both tactile detection and discrimination tasks. This is consistent with previous findings in monkeys showing that neural responses in SI and SII are modulated by working memory (Romo and Salinas, 2003) and haptic short-term memory tasks (Zhou and Fuster, 1996). Evidence from humans in favour of a role for SI in transient

storage for working memory is provided by Harris and coworkers (Harris et al., 2002). They found that participants' performance was significantly impaired when TMS was delivered over contralateral SI at specific times in the interval between stimuli to be compared. The direct involvement of SI when a memory component is required, as proposed by Harris and colleagues (2002), is compatible with the profile of results of our Experiments 1, 2, and 3. In particular, in Experiment 1 the inter-stimulus interval, given that trials with a target stimulus were randomly presented among trials with no target, could be very long (i.e., up to 30 seconds or even more), thus enhancing the memory requirement of the task – to remember what the target feels like. By contrast, in Experiments 2 and 3, a tactile stimulus was always present in each trial, and participants needed only to compare the two intervals directly (Libet et al., 1991). These differences in the inter-stimulus temporal profile in the two designs, we think, can account for the different effectiveness of TMS over SI, and in turn highlight its active role in the processing of tactile stimuli at the fingers. Electrophysiological studies of delayed match-to-sample tasks in humans have also shown the active recruitment of SI for working memory (Katus et al., 2015). These authors reported sustained activity over the contralateral primary somatosensory cortex during the retention interval, and the amplitude of this component increased with the memory load and reflected the individual memory capacity. Katus and colleagues interpreted this as evidence for the maintenance of tactile information in SI (Katus et al., 2015; see also Haegens et al., 2010; Spitzer and Blankenburg, 2011). The present results are consistent with these findings. We cannot rule out the possibility that attentional factors may also, to some extent, contribute to our effects, given that prior expectation has been shown to bias sensory representation at the early stages of the sensory processing, at least in the visual domain (Kok et al., 2013).

At this point a question remains unanswered – if not contralateral SI, then which brain region(s) support simple vibrotactile detection? A possibility is that SII is performing this task. In this respect, there is evidence that both SI and SII receive projections from the thalamus which are somatotopically organized (LaMotte and Mountcastle, 1979). Therefore,

it is possible that when SI capacity is disrupted (e.g., by TMS) SII executes some of its functions, though this is less likely considering LaMotte and Mountcastle's results (1979). Another possibility is that ipsilateral SI - with respect to the stimulated finger - is executing some of the functions of contralateral SI. Indeed, there is evidence in humans that vibrotactile stimuli elicit responses in ipsilateral SI quite early in time (for a review see Tamè et al., in press). Moreover, subcortical regions, such as, for instance, the thalamus (e.g., Vázquez et al., 2013) or the cuneate nucleus (e.g., Jörntell et al., 2014), may also significantly contribute to the processing of simple vibrotactile signals. In this respect, Libet and colleagues (1991) demonstrated that a tactile signal delivered at the level of the ventrobasal thalamus via electrodes – implanted in patients with intractable pain - can be correctly detected (more than 50% of the time), with little conscious awareness of the stimulus (Libet et al., 1991). Increasing the duration of the tactile stimuli allowed participants to be consciously aware of them. Likewise, our results suggest that, while SI is not necessarily involved in simple tactile detection (i.e., reporting stimulus presence better than chance), it may still be involved in conscious awareness of the same tactile stimuli.

7.4 Conclusion

Our results support the notion of a critical role of SI in tactile discrimination and a task-dependent role in tactile detection. Specifically, SI is required for tactile detection in the 1-IFC design, most likely because it is actively involved in maintaining a representation of the stimulus over time. This is in agreement with the “sensory recruiting” model of working memory which suggests that brain regions involved in perceptual processing, such as those devoted to vision and touch, are also actively involved in working memory maintenance of sensory information (D’Esposito, 2007; Harrison and Tong, 2009; Postle, 2006). This dissociation between the effectiveness of TMS over SI in simple detection tasks between 1-IFC and 2-IFC designs reconciles the disparity between the previous results obtained from monkeys (Romo et al., 2012) and humans (Jones et al., 2007).

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Figure Legends

Figure 1. Schematic representation of the tactile stimulation conditions in the 2IFC detection (A) and discrimination (B) tasks. TMS pulses were applied over SI or IPL in the 2IFC design at 25 and 75ms after tactile stimulus onset (C). For the 1IFC design the same timings were used for a single interval only.

Figure 2. **Activation from the functional localiser for each of 20 participants**. FMRI data show the contrast of contralateral index finger against rest, thresholded for display purposes at between $p<.05$ and $p<.01$, uncorrected for each participant. TMS sites were determined for each participant using both anatomical (postcentral gyrus) and functional (activation) criteria. The superimposed red dots represent the location of the primary motor cortex 'hotspot' (M1). Yellow dots represent the TMS site for the primary somatosensory cortex (SI: target site) and purple dots represent the TMS site for the inferior parietal lobe (IPL: control site). All participants had activation in the postcentral gyrus at least at the $p<.05$ level.

Figure 3. S**omatosensory functional localiser and TMS target sites.** Mean functional activation maps of 20 participants for contralateral finger stimulation contrasted against baseline (blue, all five fingers against baseline, $Z>2.33$, no whole-brain correction applied, but contralateral SI and bilateral SII clusters all passed family-wise error correction). The statistical maps are overlaid on the mean anatomical images of the 20 participants, transformed into the MNI template space. 95% confidence ellipsoids for the TMS target sites in MNI coordinate space (Table 2). Red: M1; Green: SI, Pink: IPL. fVOI: functional volume of interest.

Figure 4. Results of Experiment 1, 1IFC design. Participants' performance in the 1IFC ‘Yes’/’No’ detection task over time (trial window) expressed in terms of d-prime (A) and criterion (B) for the three TMS conditions (i.e., **no** TMS, SI, and IPL).

Figure 5. Results of Experiments 2-7, 2IFC design. (A) Tactile detection thresholds relative to no TMS, expressed in decibels (dB) in Experiment 2 with single-pulse

(sp)TMS over SI and IPL and (B) in Experiment 3 the same conditions with double-pulse (dp)TMS. (C) Tactile frequency discrimination thresholds expressed as the frequency difference relative to no TMS in Experiment 4 with dpTMS over SI and IPL. (D) Tactile detection thresholds relative to no TMS expressed in dB in Experiment 5 with spTMS over the median nerve (MN) and the extensor digitorum communis (EDC) and (E) in Experiment 6 the same conditions with dual-pulse TMS. (F) Tactile frequency discrimination thresholds expressed in frequency difference relative to **no** TMS in Experiment 7 with dpTMS over MN and EDC. Error bars represent the standard error of the mean (±SEM).

Tables

Table 1. Summary of the experimental designs

Experiment	Task	Type	N	TMS			Performance		Statistics	
				Pulses	Times (ms)	Targets	SI/MN	IPL/EDC	t	p
1	Detection	1-IFC ('Yes'/'No')	11	Dual	25, 75	SI, IPL	d'=1.6±0.3 C=0.34±0.15	d'=2.3±0.3 C=0.46±0.17	2.96 0.77	0.007* 0.46
2	Detection	2-IFC	12	Single	25	SI, IPL	0.15±0.57dB	0.2±0.45dB	0.02	0.99
3	Detection	2-IFC	12	Dual	25, 75	SI, IPL	2.3±0.9dB	2.4±0.6dB	0.32	0.38
4	Discrimination	2-IFC	12	Dual	25, 75	SI, IPL	82.0±6.7Hz	72.2±7.2Hz	2.11	0.029*
5	Detection	2-IFC	12	Single	0	MN, EDC	4.5±1.1dB	2.4±0.8dB	3.06	0.008*
6	Detection	2-IFC	12	Dual	0, 50	MN, EDC	6.3±1.2dB	3.2±0.8dB	2.93	0.009*
7	Discrimination	2-IFC	12	Dual	0, 50	MN, EDC	71±12Hz	40±11Hz	2.62	0.016*

Yes/No – participants made one response for target present, another for target absent; 2-IFC participants chose the interval (1 or 2) which contained the target; SI – primary somatosensory cortex; IPL – inferior parietal lobule; MN – median nerve; EDC – extensor digitorum communis. * indicates $p<.05$.

Table 2. MNI coordinates and probabilistic anatomy of TMS target sites

Target	Hem	N	MNI coordinates			Probabilistic anatomy (%) (Harvard-Oxford and Juelich atlases in FSLView)					
			x	y	z						
M1*	L	7	-49.7 (2.93)	-11.7 (7.61)	82.0 (7.83)						
	R	11	52.9 (4.32)	-7.82 (7.07)	83.5 (5.15)						
						PoCG	**PrCG**	**BA1**	**BA2**	**BA3**	**BA4a**
S1	L	9	-45.8 (7.64)	-21.1 (5.30)	54.0 (7.14)	36.8 (23.4)	21.8 (18.0)	35.7 (23.1)	25.1 (30.6)	15.4 (13.9)	21.2 (18.3)
	R	11	50.6 (4.66)	-18.2 (4.77	51.6 (7.74)	48.9 (15.0)	10.1 (15.5)	62.8 (29.1)	28.9 (28.1)	17.9 (16.1)	12.0 (15.3)
						SMG	**AG**	**LOC**	**PFm**	**PF**	**PGa**
IPL	L	9	-56.0 (5.57)	-51.6 (4.67)	36.2 (10.4)	37.6 (18.2)	31.8 (12.7)	6.78 (8.81)	42.0 (9.22)	33.1 (13.7)	27.3 (23.6)
	R	11	52.2 (5.76)	-52.4 (7.03)	43.3 (8.82)	16.6 (23.1)	42.6 (23.9)	18.2 (27.5)	41.3 (34.9)	7.82 (15.0)	38.5 (22.9)

Values are means (SD in parentheses) Hem=hemisphere; N=number of participants; MNI=Montreal Neurological Institute coordinates (MNI 152 brain, 2mm resolution, viewed in FSLView; x,y,z=coordinates in MNI space; M1=primary motor cortex target; * Coil location, outside the brain; S1=primary somatosensory target; IPL=inferior parietal lobule target; PoCG=postcentral gyrus; PrCG=precentral gyrus; BA1=Brodmann's area 1; BA2=Brodmann's area 2; BA3=Brodmann's area 3; BA4a=Brodmann's area 4, anterior division; SMG=supramarginal gyrus; AG=angular gyrus; PFm=parietal area F, medial and caudo-medial divisions; PF=parietal area F; PGa=parietal area G, anterior division