

Interhemispheric Effect of Parietal TMS on Somatosensory Response Confirmed Directly with Concurrent TMS-fMRI

Abbreviated title: Interhemispheric TMS effects on SI

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Abstract:

Transcranial magnetic stimulation (TMS) has been used to document some apparent interhemispheric influences behaviorally, with TMS over right parietal cortex reported to enhance processing of touch for the ipsilateral right hand (Seyal, Ro & Rafal, 1995). However, the neural bases of such apparent interhemispheric influences from TMS remain unknown. Here, we studied this directly by combining TMS with concurrent functional magnetic resonance imaging (fMRI). We applied bursts of 10-Hz TMS over right parietal cortex, at high or low intensity, during two sensory contexts: either without any other stimulation, or while participants received median-nerve stimulation to the right wrist, which projects to left primary somatosensory cortex (SI). TMS to right parietal cortex affected BOLD signal in left SI, with high-versus-low intensity TMS increasing the left SI signal during right-wrist somatosensory input, but decreasing this in the absence of somatosensory input. This state-dependent modulation of SI by parietal TMS over the other hemisphere was accompanied by a related pattern of TMS-induced influences in thalamus, as revealed by region-of-interest analyses there. A behavioral experiment confirmed that the same right-parietal TMS protocol of 10Hz bursts led to enhanced detection of peri-threshold electrical stimulation of the right median nerve, which is initially processed in left S1. Our results confirm directly that TMS over right parietal cortex can affect processing in left SI of the other hemisphere, with rivalrous effects (possibly transcallosal) arising in the absence of somatosensory input, but facilitatory effects (possibly involving thalamic circuitry) in the presence of driving somatosensory input.

Introduction

There are several precedents for suggesting that somatosensory processing can involve interhemispheric influences. Clinical disorders, such as somatosensory extinction or spatial neglect for the contralesional side of space (Heilman, 2003; Vallar, 1997) have often been discussed in terms of possible hemispheric ‘rivalry’ (Dambeck et al., 2006; Heilman, 2003; Hilgetag et al., 2001; Kinsbourne, 1977; Kobayashi et al., 2005; Oliveri et al., 1999b). Neuroscience studies of the normal rather than damaged brain have produced some evidence for interhemispheric influences affecting somatosensory cortex, using both invasive methods in monkeys (Iwamura et al., 1994; Iwamura, 2000; Iwamura et al., 2001), and more recently neuroimaging of apparently transcallosal influences between primary sensory cortices (Devor et al., 2007; Staines et al., 2002; Tommerdahl et al., 2006; Kastrup et al., 2008; Hlushchuk and Hari, 2006).

A pioneering study on whether interhemispheric influences may affect somatosensory processing used transcranial magnetic stimulation (TMS) to show that TMS over right parietal cortex could enhance behavioral detection of ipsilateral right-hand somatosensory stimuli (Seyal et al., 1995). Although employing only behavioral measures, the authors suggested that this finding may reflect interhemispheric influences analogous to those proposed on clinical grounds by Kinsbourne (Kinsbourne, 1977; Kinsbourne, 2003). In discussion, Seyal et al. (1995) further noted that such interhemispheric modulation might involve thalamic gating, as suggested by Heilman (Heilman, 2003) in the clinical literature.

While the Seyal et al. (1995) study clearly established that TMS over right parietal cortex can affect somatosensory processing for right-hand inputs, the neural substrates for this could not be identified in that study, since the dependent measures were purely behavioral (see also Oliveri et al., 1999a; Seyal et al., 2005). Here we aimed to study more directly the neural bases of any interhemispheric influences from right-parietal TMS on somatosensory processing in the left hemisphere for unilateral right-hand inputs, in close analogy to the classic study of Seyal et al. (1995), but now by combining TMS with concurrent functional magnetic resonance imaging (fMRI).

Although the application of TMS during fMRI is methodologically challenging, it is now technically feasible and can allow direct study of any influences of local TMS upon functional activity in remote but potentially interconnected brain regions (Bestmann et al., 2008b;Ruff et al., 2006;Ruff et al., 2008), including in the opposite hemisphere to that stimulated by TMS.

We used fMRI to measure brain responses during bursts of high (versus low) intensity TMS over right parietal cortex, during the presence or absence of suprathreshold electrical stimulation of the right median nerve, which provides input to left primary somatosensory cortex (SI), i.e., opposite to the hemisphere stimulated here by TMS. We used short bursts of TMS at 10 Hz, as this has proven effective in other recent concurrent TMS-fMRI studies from our lab (e.g. Bestmann et al., 2008b;Ruff et al., 2006;Ruff et al., 2008). Our main interest was whether high (versus low) TMS over right parietal cortex would change brain responses in contralateral left SI. If Seyal et al.'s (Seyal et al., 1995) conjecture is correct, namely that right-parietal TMS can enhance sensitivity of left somatosensory cortex to the presence versus absence of right-hand somatosensory input, then we should expect the differential effect of right median-nerve stimulation (versus no such somatosensory input) on BOLD signal in left SI to become more pronounced during right-parietal TMS. Also of interest was whether thalamic circuits might be affected, as we could study here with whole-brain fMRI.

Methods:

Five healthy males (aged 27 to 36, right handed) with no history of neurological or psychiatric illness participated. All were screened for MRI and TMS compatibility and gave written informed consent in accord with local ethics. The study was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery (University College London Hospitals National Health Service Trust) and Institute of Neurology (University College London). Our stimulation protocol conformed to published TMS guidelines (Wassermann, 1998). The scalp position for placing the TMS coil over right parietal cortex was first determined outside the scanner, using the same approach as by Seyal and colleagues (Seyal et al., 1995). For this purpose, we identified the motor hotspot for the left thenar muscles (motor threshold: mean $63.6\% \pm 4.2$ S.E.M. of TMS stimulator output) and then moved the TMS coil backwards from the motor hotspot by 2-4 cm to the first point at which there was no longer any hand contractions induced when stimulating at the high TMS intensity of 110% of the resting motor threshold. We used an intensity of 50% of the motor threshold for our low intensity TMS during the main combined TMS-fMRI experiment (see below). This motor threshold was determined inside the scanner room with the same equipment as used during scanning. While some studies suggest that cross-modal interaction can have an impact on TMS thresholds (Ramos-Estebanez et al., 2007), our main focus for the concurrent TMS-fMRI experiment here was on any interaction between the effects of high versus low TMS, during the presence or absence of concurrent tactile input to the other hemisphere (see Introduction). As described below, we found robust effects of TMS during scanning on somatosensory responses in the other hemisphere, thus confirming that our TMS protocol was effective.

A pair of surface-adhesive electrodes was positioned on the right wrist of the subject for median-nerve stimulation. Constant current pulses (square wave, 200 μ s duration) were applied to this site using a neurostimulator (DS7A, Digitimer, Hertfordshire, UK) located within a shielded box (to preclude MR artefacts) inside the scanner room. Stimulation of the right-median nerve in particular was confirmed by subjects' verbal report of sensation in the first three fingers. We ensured that the median-

nerve stimulation intensities used did not induce any twitching. For each subject, sensory threshold (mean 2.4 ± 0.16 mA) was determined by the method of limits (single pulses lasting 200 μ s), and stimulation intensity for the experiment was then set to three times that sensory threshold (7.2 ± 0.5 mA), which is clearly detectable but does not induce any muscle effects. We used such suprathreshold somatosensory stimulation to ensure that increased activation of contralateral left SI by right median-nerve stimulation could be reliably detected in fMRI (Arthurs et al., 2000;Blankenburg et al., 2003).

Our scanning experiment had a fully randomized 2 x 2 factorial design with the orthogonal factors of right parietal TMS (high versus low intensity) and right-wrist median-nerve stimulation (present versus absent). Each trial consisted of three successive ‘mini blocks’ of stimulation, each lasting 500 ms. On a random half of such trials, we applied right-wrist median-nerve stimulation in three trains of 5 pulses (each at 10 Hz). The other half of trials had no somatosensory stimulation. Orthogonally to this, TMS bursts (also 5 pulses at 10 Hz, and thus similar to the combined TMS-fMRI protocols in prior studies from our lab, see Bestmann et al., 2008b;Ruff et al., 2006;Ruff et al., 2008) were applied on each trial with either high or low TMS intensity (random half of trials each). On those 50% of trials in the 2 x 2 factorial design that had both TMS application and median-nerve stimulation on the same trial, the trains of TMS or median-nerve stimulation (both 5 pulses at 10Hz) were temporally interleaved with a 180-degree difference in phase. Thus, each such trial started with a TMS pulse, followed 50 ms later by the first somatosensory stimulation, followed 50 ms later by the next TMS pulse and so on. After each trial, a rest period without any stimulation (neither median nerve nor TMS) was included, lasting four image volumes.

Functional data were acquired on a 1.5T whole-body scanner (Magnetom Sonata, Siemens Medical System, Erlangen, Germany), operating with the standard CP receive head and body transmit coil. We used a multi-slice gradient echo EPI sequence (39 slices, 64 x 96 matrix (readout x phase-encoding), in-plane resolution: 3 x 3 mm, 2 mm slice thickness, 50% spatial gap between adjacent slices, TE=50ms, TR=2880 ms, 2298 Hz/pixel bandwidth, echo spacing 500 μ s). In addition, oversampling (50%) was used in the phase-encoding direction to shift any possible ghost artifact induced by mere presence of the TMS coil outside of the volume of interest. The last seven slices (33-39, lasting

630 ms) were recorded without an MR excitation high frequency pulse. This enabled us to apply the TMS-pulses and the somatosensory stimulation always within this period, hence without any potential corruption of functional image volumes. In addition, this ensured a constant auditory input from the scanner, as gradients during these slices remained turned on. The acquisition time for one volume was 3.51 sec. Two sessions were acquired for each subject (each session comprised 320 volumes, including 5 dummy scans to allow T1 saturation). We chose to compare high-intensity (effective) TMS versus low-intensity (less effective or ineffective) TMS at a single right-parietal site, similar to the site used by Seyal et al. (1995), rather than comparing different TMS sites, due to the technical problems that relocating the TMS probe within an fMRI session would inevitably cause. Moreover, the appropriateness of high versus low TMS comparisons at a given site during concurrent fMRI has recently been established by other studies from our group using similar concurrent TMS-fMRI protocols (Bestmann et al., 2008b; Ruff et al., 2006).

Each session included 44 randomly intermingled trials, 11 per condition in the 2 x 2 design. To preclude visual changes (e.g., from blinks), subject kept their eyes closed throughout scanning. In addition, to ensure that TMS could not lead to any changes in performance that might otherwise have complicated interpretation of the physiological fMRI data, subjects had no behavioural task during scanning (see also Ruff et al., 2006). Thus, as per the Introduction, our a-priori aim was to test for a physiological interaction of right parietal TMS with right-wrist somatosensory input, in terms of the BOLD response of left SI (and possibly the thalamus as well: see below). Nevertheless, we also ran a behavioral follow-up experiment outside the scanner (see below), which confirmed that our particular right-parietal TMS protocol, using bursts at 10Hz, could indeed produce the same behavioral effect originally documented by Seyal et al, (1995), namely enhancement of somatosensory detection on the ipsilateral right hand.

TMS during scanning was applied using a Magstim Super Rapid stimulator and MR-compatible non-ferrous figure-of-eight coil with a small-diameter (30mm inner diameter, 70mm outer diameter, 15 turns each winding, wire size 5x1.5mm, 22.9 μ H inductance, 4.7kVA predicted maximal current at 100%) from the MAGSTIM Company, Dyfed, UK. The coil was positioned over the stimulation site tangentially to the scalp, at

approximately 45° from the midline, inducing a biphasic current with an initial anteroposterior direction. We ensured that TMS did not induce any muscle twitches in the experiment (see above for TMS-site selection). The coil was held fixed by a non-ferromagnetic custom-built coil holder, and the participant's head was fixed with vacuum cushions. To avoid any radio-frequency interference of TMS with image acquisition, the TMS-stimulator was placed in a shielded metal cabinet in the scanner room, and the TMS cable was passed through a custom filter box (the Magstim Company, Dyfed, UK) and further ferrite sleeves (Wuerth Elektronik, Waldenburg, Germany); see also (Bestmann et al., 2008b;Ruff et al., 2006;Ruff et al., 2008). Furthermore, the TMS coil was connected to the stimulator in parallel to a high voltage relay (Magstim ES9486, The Magstim Company). During volume acquisition, this relay was closed, shorting any potential leaking-current. Thus, any current flow through the stimulation coil originating from the stimulator was eliminated while it waited to release a pulse. The relay was opened 50 ms prior to a TMS train, and closed 11 ms after the last TMS pulse of a train.

All stimuli were controlled using the MATLAB (The Mathworks, Natick, Massachusetts, USA) toolbox Cogent 2000 (<http://www.vislab.ucl.ac.uk/Cogent/>), running on a conventional PC. Image processing and analysis was performed with SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). Functional images were reconstructed offline, and the first five images of each run discarded to avoid T1 equilibration effects. In accord with the standard SPM approach, the remaining functional images were realigned to the first of the series, corrected for movement-induced image distortions, normalized to the MNI anatomical standard space and spatially smoothed with a 9 mm FWHM Gaussian kernel in accord with the standard SPM approach. In addition, the fMRI data were temporally band-pass filtered (lower/upper cutoff-frequency at 7 and 128 sec, respectively).

Statistical parametric maps were calculated by multiple regressions of the data onto a model of the hemodynamic response (Friston et al., 1995). This model contained regressors for the onsets of every 'mini-block' for each of the four conditions in the 2x2 design, convolved with the canonical hemodynamic response function in SPM2. An autocorrelation model was used in order to account for scan-to-scan dependencies in the error term. Statistical inference used a fixed effect model, in accord with the limited number of subjects (n=5) available for this demanding combined TMS-fMRI protocol.

However, we also inspected individual data to ensure that the critical fMRI pattern was observed for all subjects (see below). For unrestricted whole-brain analyses we used a threshold of $p < 0.05$, family-wise error (FWE) corrected for the entire image volume. For analyses of activity in brain areas for which we had clear *a priori* hypotheses (e.g., left somatosensory cortex and thalamus, see Introduction), critical effects were inspected in volumes-of-interest (VOIs) derived either by anatomical criteria (e.g., the thalamus was defined by means of a computerized cytoarchitectonic atlas, see http://www.loni.ucla.edu/ICBM/Downloads/Downloads_Atlases.shtml), or functionally by inclusive masking with an orthogonal contrast used to define specific brain areas of interest (e.g., activation for presence minus absence of right-hand median-nerve stimulation was used to confirm functional localization of contralateral left somatosensory cortex). The results of these hypothesis-driven analyses are all reported at a threshold of $p < 0.05$, FWE-corrected for the VOI (Worsley et al., 1996).

Here we used bursts of TMS at 10Hz during scanning in order to drive reliable BOLD responses by the TMS (Bestmann et al., 2008b; Ruff et al., 2006; Ruff et al., 2008). Our particular TMS protocol thus differed from the original Seyal et al. (1995) study, which had used single-pulse TMS. Accordingly, we also conducted a new psychophysical study outside the scanner that sought to replicate the classical behavioral findings of Seyal et al (1995), but now using the identical 10Hz-burst TMS protocol as in our concurrent TMS-fMRI study. This follow-up behavioral experiment was conducted in 4 additional subjects, who were again screened for TMS compatibility and gave written informed consent in accord with local ethics. Briefly, we applied 5 pulses of 10 Hz rTMS at the outset of each trial, either at 110% or 50% of motor threshold, as during scanning. The TMS coil was again localized over right parietal lobe, using the identical procedure as for the main fMRI experiment. On a random half of these trials, peri-threshold right median nerve stimulation (of the same duration and timing relative to TMS burst as for the fMRI experiment) was applied during TMS. On the other half of trials, TMS was applied in the absence of median nerve stimulation. After each trial, subjects were asked to respond by button-press whether right-hand tactile stimulation was present or not. Subjects each completed 4 blocks of 60 trials. Tactile stimulation intensity was determined separately for each block, with the aim of keeping the intensities peri-

threshold. Some blocks were removed from analysis because of greater than 90% accuracy (3 blocks), a bias towards responding 'absent' on more than 90% of trials (2 blocks), or a technical malfunction (2 blocks). Nine blocks remained, yielding a total of 540 trials. Sensitivity (d') and response bias (criterion) were calculated for each retained block, and paired t-tests were performed to determine the effect of TMS intensity on d' across blocks.

Results

Concurrent TMS-fMRI experiment

Main effect of right median-nerve stimulation on BOLD signal

We first considered BOLD-signal changes due to presence (minus absence) of median-nerve stimulation on the right wrist, which would be expected to activate left somatosensory cortex and related regions. This contrast did indeed show the expected highly significant activation of contralateral left SI (peak at X=-38, Y=-38, Z=66) and also SII (X=-50, Y=-20, Z=22); see Figure 1. We also found some activation of left thalamus due to contralateral right median nerve stimulation, with a peak at X=-4, Y=-12, Z=6.

Main effect of high versus low right-parietal TMS

The main effect of high- minus low-intensity TMS over right parietal cortex, revealed activations very similar to those found in prior combined TMS-fMRI studies for such contrasts (Bestmann et al., 2008b; Ruff et al., 2006; Ruff et al., 2008), mainly auditory cortices (peak at X=60, Y=-14, Z=12 and X=-58, Y=-28, Z=22) due to the slightly louder ‘click’ sound associated with higher intensity TMS, as would be expected. More interestingly, we also found some activation of the thalamus (peak at X=-10, Y=-18, Z=8), a point we will return to. However, we did not find reliable BOLD-signal changes within right parietal cortex, over which the TMS coil was placed. Previous concurrent TMS-fMRI studies indicate that MR signal-to-noise immediately under the TMS coil does not always allow BOLD effects to be uncovered there (Bestmann et al., 2008a)

Interaction of high versus low right-parietal TMS with presence versus absence of right median-nerve stimulation

Our main question of interest, given the prior study of Seyal et al. (1995), concerned the possible interaction between high versus low intensity right-parietal TMS and presence versus absence of somatosensory input to the right median-nerve that projects to contralateral left SI. In particular, as described in the Introduction, we aimed to test

whether high versus low right-parietal TMS could enhance the selective response of left somatosensory regions to the presence versus absence of right-wrist somatosensory input. This should be expressed as a specific interaction between TMS intensity and median-nerve stimulation, namely: high minus low TMS during median-nerve stimulation should lead to stronger BOLD increases than high minus low TMS without median-nerve stimulation. To assess this for brain regions specifically responding to right median-nerve stimulation, as per our hypothesis, we examined this interaction within a VOI representing the regions activated by median-nerve stimulation (thresholded at $p < 0.05$ FWE corrected, see Figure 1). Please note that this VOI approach can only make our analyses more conservative, by requiring the reported regions to pass a further test in order to confirm the specificity of their response pattern.

Within those brain regions already showing a main effect of presence minus absence of right median-nerve stimulation (Figure 1), we found an interaction of TMS intensity with presence/absence of median-nerve stimulation for left SI (peaking at $X = -38$, $Y = -24$, $Z = 64$); see Figure 2A-C. The plot in Figure 2D shows the mean percent BOLD signal change in this left SI region (see Figures 2 A-C) for each of the 4 conditions. This plot shows that high versus low intensity TMS over right parietal cortex enhanced the BOLD signal of left SI during the *presence* of right median-nerve stimulation (see fourth and rightmost bar in plot of Figure 2D, comparing this with the third bar); whereas the same high versus low TMS over right parietal cortex tended instead to reduce BOLD signal in left SI when applied in the *absence* of right-median nerve stimulation (compare second and first bars in plot of Fig 2D). Note that this interaction was highly reliable across subjects, as the very same pattern was found for each of the five individual participants when inspecting their BOLD signal changes (mean coordinates of individual interaction peaks \pm SEM: $X = -36 \pm 2$, $Y = -32 \pm 3$, $Z = 62 \pm 2$) within the left SI cluster that had responded to right-median nerve stimulation in the group analysis (Figure 1). Hence, our data indicate that the differential response of left SI to presence versus absence of right-median nerve somatosensory input was significantly strengthened by high versus low right parietal TMS, thus providing a BOLD outcome that is logically analogous to Seyal et al.'s (Seyal et al., 1995) purely behavioral findings;

see also the results from our own behavioural follow-up study below, using our 10 Hz-burst TMS protocol.

Possible role of thalamus in interplay between right parietal TMS and left SI

Given that the thalamus had shown an effect (see earlier) in response to right median-nerve stimulation (and had also been discussed by Seyal et al (Seyal et al., 1995) as being potentially involved in interhemispheric effects of cortical TMS on somatosensory processing), we also conducted a VOI analysis of BOLD signal in the thalamus. For this purpose, we used a computerized cytoarchitectonic atlas (see Methods) to define anatomical VOIs corresponding to the thalami in both cortical hemispheres, and then applied small-volume correction (Worsley et al., 1996) to assess any significant ($p < 0.05$ FWE-corrected) interaction of TMS intensity and median nerve stimulation within these thalamic VOIs. This analysis revealed regions in the right and left thalamus (peaks at $X=10, Y=-22, Z=8$ and at $X=-12, Y=-8, Z=6$, see Figures 3A-C) that showed similar activity changes to those found for left SI as reported above, albeit now primarily due to a substantial increase in BOLD signal when high right-parietal TMS was combined with right median-nerve stimulation. Figure 3D plots the corresponding percent signal changes for the different conditions, confirming that BOLD signal in the left thalamus is boosted in the conjoint presence of right median-nerve stimulation and high-intensity right parietal TMS. This pattern was also consistent across all participants (as confirmed by inspecting BOLD changes within the thalamic VOI at each individual's peak). Finally, Figure 3E shows the equivalent group results for the right thalamus, i.e., now in the same hemisphere as the TMS-stimulated right parietal cortex. Strikingly, this region also showed increased BOLD when high-intensity right parietal TMS was combined with right-hand somatosensory input (again consistently in all subjects, as confirmed by individual inspection). This finding suggests that bilateral thalami may start to influence each other interhemispherically, in the specific context of combined right-wrist somatosensory input and right-parietal TMS, as part of a cortico-thalamic circuit influencing the two hemispheres.

Behavioral Follow-up Experiment

As predicted from our new BOLD findings, and consistent with the classic purely behavioral study by Seyal et al. (1995), our follow-up study found that our 10-Hz burst, right-parietal TMS protocol significantly enhanced ipsilateral somatosensory detection, for peri-threshold right median-nerve stimulation. Sensitivity (d'), as calculated by signal detection theory, for this right-hand stimulation was significantly enhanced by high-versus low-intensity TMS at 10 Hz, in a manner that was consistent across blocks (high-intensity TMS: $d' = 0.64$; low-intensity TMS: $d' = 0.18$; $t(8) = 2.46$, $p = 0.039$). Sensitivity for high-intensity TMS trials was significantly greater than zero ($t(8) = 4.05$, $p = 0.0037$), whereas the sensitivity on low-intensity TMS trials was not ($t(8) = 0.68$, $p = 0.52$). By contrast, TMS intensity did not affect response bias (high-intensity TMS: criterion = -0.24 ; low-intensity TMS: criterion = 0.21 ; $t(8) = -0.67$, $p = 0.52$; neither criterion differed significantly from zero; both p 's > 0.49). Thus, the same TMS protocol as we used during concurrent fMRI was shown to reproduce Seyal et al.'s (1995) classic behavioral finding of enhanced sensitivity for detecting ipsilateral right-hand touch.

Discussion

While it is well accepted that somatosensory input projects contralaterally to primary somatosensory cortex (SI), there has been increasing interest in possible interhemispheric interplay in somatosensory processing, both clinically (e.g. see Oliveri et al., 1999b; Remy et al., 1999; Sarri et al., 2006; Kobayashi et al., 2005) and within basic neuroscience (e.g. Calford and Tweedale, 1990; Kastrup et al., 2008; Devor et al., 2007; Hlushchuk and Hari, 2006; Iwamura et al., 1994; Kanno et al., 2003; Nihashi et al., 2005; Noachtar et al., 1997; Staines et al., 2002; Tommerdahl et al., 2006). In a purely behavioral study, Seyal and coworkers (Seyal et al., 1995) had demonstrated that TMS over right parietal cortex can benefit somatosensory processing for the ipsilateral (right) hand (see also Oliveri et al., 1999a; Seyal et al., 1997; Seyal et al., 2005). In their classic 1995 paper, Seyal and colleagues suggested that this may potentially reflect interhemispheric influences of right parietal TMS on left somatosensory cortex, perhaps arising transcallosally and/or via the thalamus. But since they used only behavioral measures, they could not directly ascertain the neural basis of possible interhemispheric TMS effects.

Here we combined TMS with concurrent fMRI (see also Bestmann et al., 2008b; Ruff et al., 2006) to directly study the neural processes underlying interhemispheric effects of TMS to right parietal cortex. Like Seyal et al (1995), we used an on-line TMS-approach (rather than off-line TMS), applying TMS during the presence or absence of somatosensory input to the ipsilateral hand, but now combining this with fMRI. We could therefore study the immediate impact of TMS on BOLD activity in SI of the opposite hemisphere, during the presence or absence of concomitant tactile input to that hemisphere. This allowed us to show directly that applying high- versus low-intensity TMS over right parietal cortex (with this TMS-site selected similarly to (Seyal et al., 1995), can indeed change the response of left SI to somatosensory input on the right hand. Specifically, such TMS enhanced the BOLD signal for left SI in response to right median-nerve stimulation, while tending to have the opposite effect of reducing left SI BOLD signal when no right-hand stimulation was present (see Figure 2). This same interaction pattern was observed for each individual participant that we scanned. Another

way of stating the interaction outcome is that the effect of presence versus absence of right-hand stimulation was enhanced for left S1 during right parietal TMS, thus somewhat analogous to Seyal et al.'s (1995) finding that presence versus absence discrimination for right-hand touch could be enhanced by right parietal TMS. Moreover, in our behavioural follow-up study, we were able to replicate Seyal et al.'s finding of enhanced detection sensitivity for right-hand touch, during our high intensity versus low intensity right-parietal TMS, using exactly the same 10 Hz TMS protocol that we had used during concurrent fMRI.

The interaction in the fMRI data for left SI here, in the hemisphere opposite to the right-parietal TMS represents a 'state-dependent' remote physiological effect of TMS (see also Bestmann et al., 2008b; Ruff et al., 2008), for possible analogs in recent concurrent TMS-fMRI studies of the motor or visual systems, respectively). Thus, the effect of local TMS applied to right parietal cortex on remote yet interconnected regions (such as left SI) depended here on the current context, i.e. whether or not somatosensory input was given concurrently to the right hand. There may be alternative physiological explanations for these observed remote effects, depending on whether TMS may have functionally disrupted activity in the right PPC or increased cortical excitation under the TMS coil. On the latter possibility, the reduction in BOLD signal for left SI caused by right-parietal TMS when applied in the absence of any concurrent somatosensory input to the right hand (see Figure 2D, second versus first bar in that plot) might potentially reflect interhemispheric inhibition that may arise transcallosally, as suggested for some other somatosensory paradigms, including invasive animal studies of transcallosal effects (e.g. Clarey et al., 1996) and more recent human neuroimaging studies (e.g. Devor et al., 2007; Kastrup et al., 2008; Hlushchuk and Hari, 2006). Such interhemispheric inhibition might potentially be mediated by stimulation of transcallosal fibres targeting GABAergic interneurons in the opposite hemisphere, as has been well established for the motor cortex (Daskalakis et al., 2002). Possible pathways for such an influence in the present experiment might be via transcallosal connections between Brodmann areas 1 or 2, and/or motor cortex (Killackey et al., 1983).

The strikingly opposite pattern observed when applying the same right-parietal TMS during right-median nerve stimulation, with high-intensity right-parietal TMS now

enhancing BOLD signal for left SI in response to the somatosensory input to the right hand (see Figure 2D), may relate to cortico-thalamic interplay (as already speculatively proposed by Seyal et al., 1995). When using a VOI analysis of the thalamus here, we found that the thalamus showed a somewhat similar interaction pattern to left SI (specifically with higher BOLD signal when high-intensity TMS was combined with the median-nerve stimulation). Localization of this thalamic effect encompassing the ventroposterior nucleus (see Figure 3), which is known to respond to tactile stimulation (Malinen et al., 2006). However, some caution has to be applied when attributing BOLD signal changes to specific thalamic nuclei (such as tentatively for the ventroposterior nucleus here), due to anatomical and functional intersubject variability (Davis et al., 1998). Nevertheless, a number of studies have indicated that activation of SI (Ergenzinger et al., 1998; Li et al., 2005) and/or the PPC as one component of an attentional network (Crick, 1984) can lead to re-activation of the thalamus, either directly via relay neurons, or indirectly due to disinhibition by the nucleus reticularis. The latter is a net-like structure that enfolds the thalamus, comprising inhibitory neurons that can gate thalamic relays (Heilman, 2003). Animal tracing studies indicate reticuloreticularis connections between thalami in either hemisphere (Battaglia et al., 1994; Chen et al., 1992; Raos and Bentivoglio, 1993), potentially consistent with the bilateral thalamic pattern found here functionally. Interhemispheric effects on thalamic gating, driven by TMS stimulation of right parietal cortex when the thalamus is also receiving sensory input, may thus contribute to the interactions between hemispheres found when TMS is combined with somatosensory input, as here.

Although our concurrent TMS-fMRI study found robust *remote* effects of right-parietal TMS upon BOLD signals elsewhere (specifically in contralateral S1 and in bilateral thalamus, where state-dependent effects of TMS were found that interacted with the presence or absence of concurrent right-hand touch) we did not find any reliable BOLD signal changes under the TMS coil itself, in right parietal cortex. This particular outcome should be treated with some caution, since it is essentially a null result, and other recent TMS-fMRI studies have indicated that MR signal-to-noise can sometimes be reduced immediately under the TMS coil (see Bestmann et al., 2008a). But this does not undermine our clear effects on remote areas, including in the hemisphere opposite to

TMS application, which thus clearly demonstrate an interhemispheric influence of the right-parietal TMS. While it might be interesting in future work to extend the paradigm we have introduced to address a more ‘extinction-like’ situation with bilateral somatosensory inputs projecting to both hemisphere, for the present purposes of demonstrating a clear interhemispheric effect, it was a virtue to apply TMS to one hemisphere while stimulating the other unilaterally with somatosensory input. Moreover, in this respect our study remained closely analogous to the classic Seyal et al. (1995) study, which likewise applied TMS to right-parietal cortex while examining the impact for somatosensory inputs applied unilaterally to the ipsilateral hand.

In conclusion, our data confirm directly that TMS applied over one hemisphere (here, right parietal cortex, as in Seyal et al., 1995) can affect somatosensory responses in the other hemisphere (here, left SI). These remote effects of right-parietal TMS apply in a manner that depends on concurrent somatosensory input to the right hand (ipsilateral to TMS), and may relate to cortico-thalamic circuitry as well as transcallosal connections. More generally, concurrent TMS-fMRI can show causal influences of local TMS upon brain activity in remote but interconnected regions in the opposite hemisphere that can vary in a state-dependent manner.

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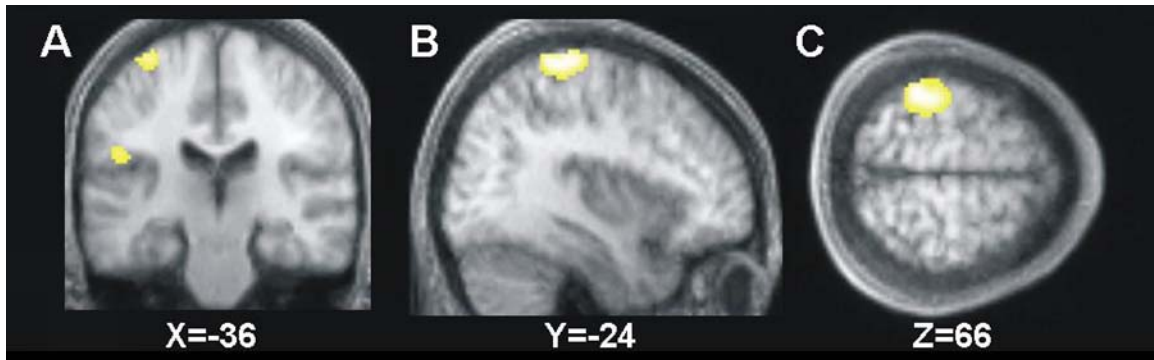


Figure 1

Main effect of presence minus absence of right-hand somatosensory stimulation (electrical stimulation of right median nerve) shows highly significant activations ($p < 0.05$ FWE corrected) in contralateral SI (the dorsal activation visible in A-C) and SII (ventral activation visible here in A only). The activations are projected onto (A) coronal; (B) sagittal; and (C) transverse slices of the averaged structural scans of all subjects.

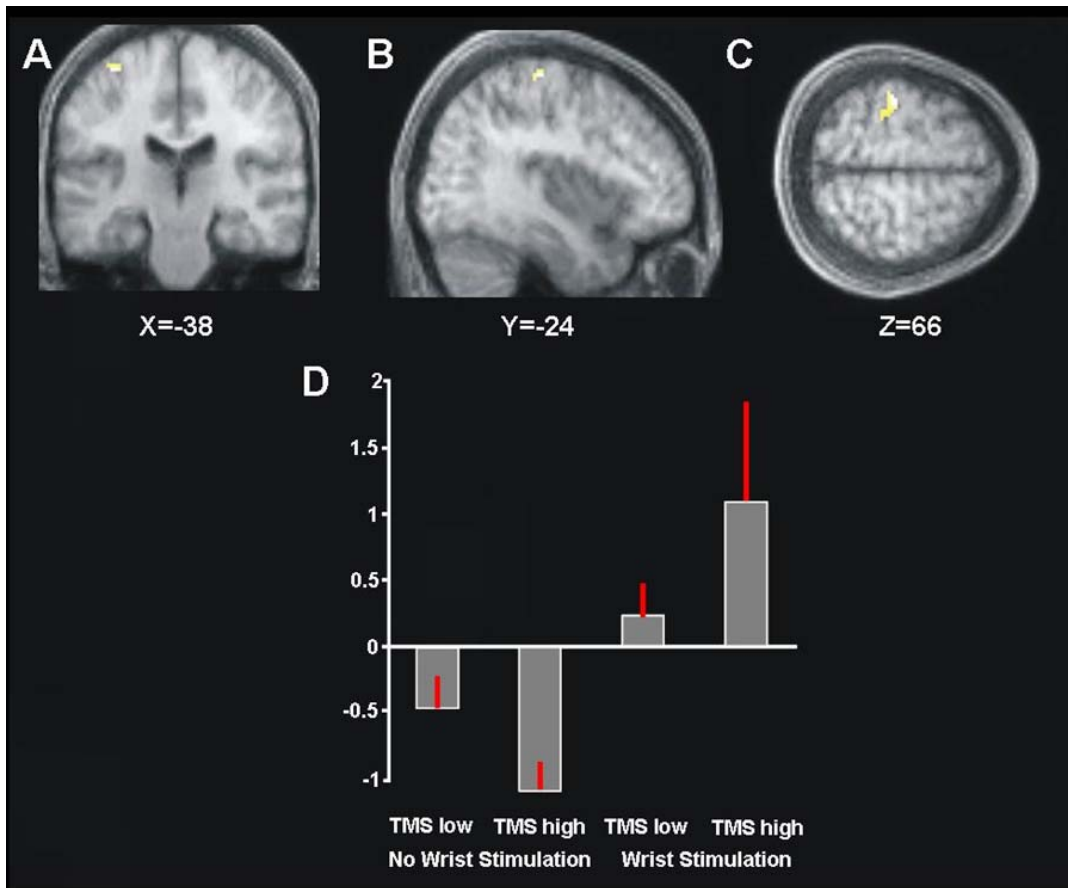


Figure 2

(A-C) Areas showing an interaction between high- minus low-intensity right-parietal TMS, and presence minus absence of right-median nerve sensory stimulation, within regions responding to right median-nerve stimulation overall (cf. Figure 1). Significant ($p < 0.05$, FWE-corrected) interaction effects shown on (A) coronal; (B) sagittal; and (C) transverse slices of the averaged structural scans. Left SI is clearly implicated. (D) Plot of mean percent BOLD signal change extracted from the left SI cluster of the interaction contrast shown in (A-C). High- versus low-intensity TMS over right parietal cortex increased BOLD signal for left SI during right median-nerve stimulation (compare fourth bar to third), but the same high TMS decreased BOLD signal for left SI in the absence of somatosensory input (compare second bar to first). Restated, high-intensity right-parietal TMS increased the differential response of left SI to the presence versus absence of right-hand stimulation (compare fourth and second bars in the histogram), as compared with low-intensity TMS (compare third and first bars).

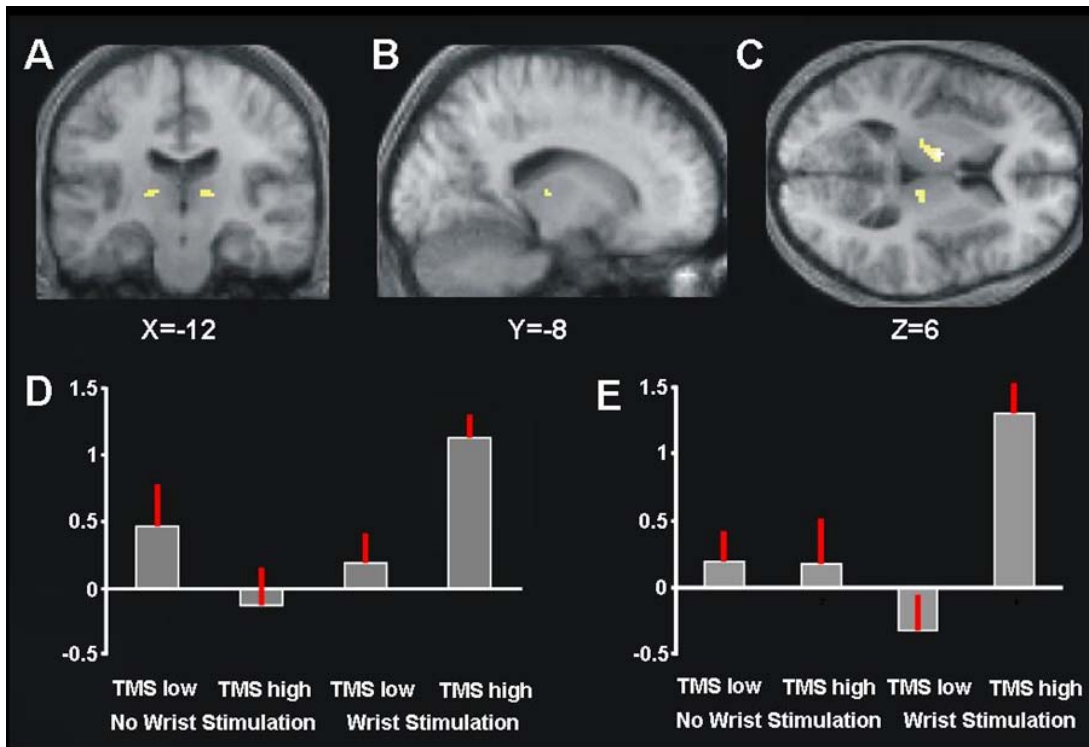


Figure 3

VOI analysis of the thalamus, as defined by a cytoarchitectonic postmortem atlas (see main text). Panels (A-C) show the SPMs for the interaction of TMS and median nerve stimulation within the thalamus ($p < 0.05$ FWE corrected for that volume of interest), overlaid onto the mean structural scan. Panels (D-E) show plots of the group mean percent BOLD signal change from the left (D) and right (E) thalamic clusters for each condition in the interaction of TMS intensity and right wrist stimulation. BOLD signal in the thalamus was highest during combined right-hand somatosensory stimulation and high intensity TMS over right parietal cortex (fourth bar in each histogram).