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Testing the inter-hemispheric competition account of visual extinction with combined TMS/fMRI

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ABSTRACT

Theoretical models of visual neglect and extinction entail claims about the normal functioning of attention and parietal cortex in the healthy brain: (1) 'pseudoneglect', a commonly observed attentional bias towards left space, reflects the greater dominance of parietal cortex activity of the right versus left hemisphere; (2) the capacity to distribute attention bilaterally depends causally on the relative balance of parietal activity between the hemispheres; (3) disruption of the dominant right parietal cortex shifts this inter-hemispheric balance leftward, causing a rightward shift in attentional bias. We tested these claims using low-frequency offline transcranial magnetic stimulation (TMS) to transiently inhibit activity in the right angular gyrus/intra-parietal sulcus, followed by a visual detection task to assess changes in attentional bias, and functional magnetic resonance imaging (fMRI) to test for the predicted leftward shift in brain activity. The task required participants to covertly monitor both hemifields to detect and report the location of upcoming transient visual targets that appeared on the left, right or bilaterally. In the behavioural experiment, participants exhibited a leftward attentional bias ('pseudoneglect') at baseline, which was abolished by TMS. In the fMRI experiment, participants activated an expected network of visual, parietal and frontal cortex bilaterally during the period of covert bilateral attention. TMS shifted the relative hemispheric balance of parietal activity from right to left. The consistent direction of TMS-induced behavioural and functional change indicates a causal role for parietal inter-hemispheric balance in distributing visual attention across space.

1. Introduction

Following injury to right parietal cortex, patients often exhibit visual attentional dysfunction, such as neglect of stimuli in left space. In a related syndrome, extinction, processing of left stimuli is intact, but if presented simultaneously with a stimulus on the right, the stimulus on the right is detected while that on the left is 'extinguished' from awareness. Theoretical models of the pathophysiology of neglect and extinction emphasise the critical role of relative hemispheric dominance and inter-hemispheric competition in controlling the allocation of attention across space (Cohen et al., 1994; Heilman and Van Den Abell, 1980; Kinsbourne, 1977; Mesulam, 1981). The inter-hemispheric competition model posits that the left and right parietal cortices compete to direct attention towards contralateral hemispace, with each hemisphere exerting an inhibitory influence over the other. In a healthy brain, these competing attentional vectors are thought to be broadly counterbalanced, enabling attention to be distributed across both hemifields. However, correlative evidence from brain imaging in healthy volunteers suggests that the right inferior parietal lobe is dominant over the left during bilateral attention (Cicek et al., 2007), consistent with the greater severity of attentional impairments after right than left injury (Weintraub and Mesulam, 1987). Right parietal damage both directly weakens leftward attention, and indirectly, via transcallosal disinhibition, leads to hyper-activation of left parietal cortex, consequently exacerbating a rightward attentional bias. Thus, disrupted parietal inter-hemispheric balance is thought to deviate attention rightward, resulting in a competitive advantage for right hemifield stimuli during tasks that require bilateral attention (de Haan et al., 2012).

Brain imaging and brain stimulation studies have confirmed a role for disrupted inter-parietal hemispheric balance in

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contributing to neglect/extinction in the damaged brain (Corbetta et al., 2005; Corbetta and Shulman, 2002; Koch et al., 2008). However, these models of pathology also make claims about normal function: specifically, that it is the relative balance of activity between left and right parietal cortex that causally mediates bilateral spatial attention. Brain imaging studies have provided confirmatory correlative evidence that participants' behavioural bias between left and right space relates to measures of functional lateralization within attention structures (Benwell et al., 2014; Szczepanski and Kastner, 2013; Thiebaut de Schotten et al., 2011). Causal evidence has come from studies using non-invasive transcranial magnetic stimulation (TMS) to transiently perturb function in parietal cortex. Based on the observed pattern of TMS-induced behavioural interference, inferences have been made about the presumed nature of functional interactions between left and right parietal cortex.

The first two TMS studies of this kind used a visual detection task, designed to mimic clinical confrontation testing of extinction, combined with online high-frequency (Pascual-Leone et al., 1994) or offline low-frequency TMS (Hilgetag et al., 2001). Participants had to monitor both hemifields simultaneously to detect upcoming transient targets, which appeared either on the left, right or bilaterally. In both studies, right parietal TMS impaired detection performance on bilateral trials. In Hilgetag et al.'s study, behaviour was assessed before and after 10 min of 1 Hz TMS applied at rest. The key finding was that right parietal TMS induced a rightward shift in the spatial distribution of participants' errors on bilateral trials. That is, on trials in which participants failed to detect both targets, after TMS they were more likely to detect only the target on the right and omit that on the left, similar to clinical extinction. Subsequent behavioural TMS studies have replicated the finding that right parietal interference impairs detection of left stimuli on bilateral trials (Dambeck et al., 2006; Duecker and Sack, 2014; Meister, et al., 2006). However, the functional basis of impaired performance on bilateral trials is unclear, since an attention deficit for left space would itself compromise bilateral trials, which are the most attentionally demanding and therefore the most sensitive trial type. Hence, existing TMS evidence for a specific causal role of parietal inter-hemispheric balance in mediating bilateral attention currently relies on reverse inference from behavioural impairments and is therefore weak.

Rather than inferring function from behaviour, we combined TMS with fMRI to test directly the hypothesis that normal bilateral attentional function depends on the balance of activity between left and right parietal cortex. We used a visual target detection task previously used to simulate extinction using TMS in the healthy brain (Hilgetag et al., 2001). The aim was to use a task in the MRI scanner that would provide a sensitive means of detecting changes in the balance of parietal inter-hemispheric competition caused by TMS, even if any behavioural effects are likely to be subtle or short-lived.

We targeted stimulation at the caudal part of the angular gyrus (ANG) at the junction with the intra-parietal sulcus (IPS). We therefore refer to the TMS protocol as targeting right ANG/IPS. Stimulation was applied to the right hemisphere, given the dominance of right parietal cortex over left in extinction and neglect (Becker and Karnath, 2007; Cicek et al., 2007), and since previous TMS studies have implicated this region in attention (Ashbridge et al., 1997; Rushworth et al., 2001) and shown that stimulation at this site can induce extinction-like behaviour in healthy individuals.

First, we functionally localised a region of right posterior parietal cortex in each individual at which online high frequency repetitive TMS (10 Hz, 500 ms) disrupted attentional performance (Ashbridge et al., 1997). Anatomical mapping confirmed that this 'hotspot' was located in the caudal part of the right ANG at the junction with the IPS. In a subset of participants, we then confirmed that offline low frequency TMS (1 Hz, 15 min) to that brain region induced extinction-like behaviour in an orthogonal visual detection task. Whereas TMS did not change detection accuracy, the spatial distribution of errors on bilateral trials was shifted from left to right, simulating clinical visual extinction and replicating the key finding of Hilgetag et al. (2001). We then conducted the main fMRI experiment, in which participants performed the same visual detection task, once before and after 1 Hz TMS was applied to transiently inhibit function of the right ANG/IPS. Given the behavioural finding that this stimulation protocol shifted attentional bias from left to right, we analysed the functional imaging data to test the hypothesis that right ANG/IPS TMS would shift the parietal inter-hemispheric balance from right to left.

2. Methods

2.1. Participants

Five right-handed individuals participated in the behavioural TMS experiment (4 male, mean age = 23.8 years, SD = 4.7). Twelve right-handed individuals participated in the main TMS/fMRI experiment (4 male, mean age = 25.9 years, SD = 3.5), four of whom also underwent the behavioural TMS experiment. All participants gave written informed consent as approved by the Central Office for Research Ethics Committee (COREC reference number: 05/Q1606/96). All participants had normal or corrected-to-normal vision and indicated no family history of psychiatric or neurological disease. No participant reported any side effect from the experimental procedure.

2.2. TMS functional localisation of right posterior parietal cortex

All participants in both experiments first underwent a 2-h functional localizer session to determine the anatomical target for TMS in each individual. To identify the sub-region of right angular gyrus/intra-parietal sulcus (rANG/IPS) at which stimulation would disrupt attentional function, participants underwent an established mapping protocol previously shown to identify parietal regions functionally involved in the allocation of visual attention (Ashbridge et al., 1997; Rushworth et al., 2001). That location was then targeted for TMS in the main experiments.

Each trial of the functional localisation procedure started with an alerting tone and a white fixation spot (500 ms) at a random location on the screen, followed by the search array (750 ms), composed of red and green diagonal lines on a black background (Fig. 1A). The target was a red line oriented at 45°, surrounded by two kinds of distracters – green lines oriented at 45°, and red lines oriented at 135°. The target was present on half of trials. Participants were instructed to respond on each trial with a right index finger button press if they detected the target and a right middle finger button press if not. The inter-trial interval lasted until participants responded or up until 4 s maximum. The visual search task was run on a computer with a Windows 98 operating system (75 Hz refresh rate 1024×768 resolution) triggered by Turbo Pascal (Version 7.0, Borland International, Inc).

Each participant first performed 10 practice task blocks (10 trials per block), the last 5 of which were performed with sham TMS (coil placed on the head but oriented away), in order to habituate participants to the somatosensory and acoustic artefacts of the subsequent TMS procedure. Earplugs were worn throughout. Participants then performed blocks of the search task, during which a train of high frequency TMS (10 Hz, 500 ms, 65% maximum stimulator output, 70 mm coil) was applied time-locked to search array onset. TMS blocks alternated with baseline blocks, in

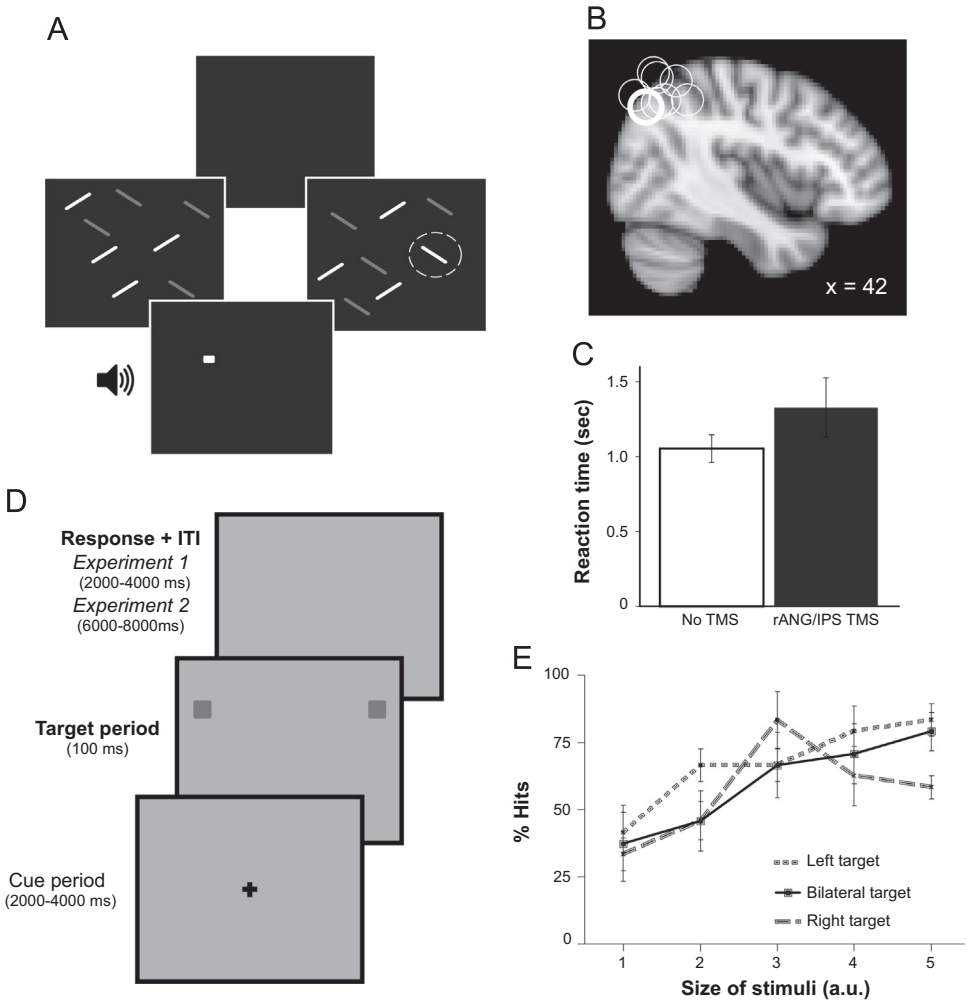

Fig. 1. Functional localisation of parietal cortex and the visual extinction task. Panels A–C illustrate components of the functional localization procedure (devised by Ashbridge et al., 1997) used to identify a sub-region of right ANG/IPS functionally involved in the allocation of visual attention. (A) Schematic of the conjunction visual search task. A trial began with an alerting tone and a fixation cross (500 ms) at a variable location on the screen, followed by the search array (750 ms). Participants had to detect and report the presence or absence of a singleton target (red line oriented at 135° indicated by the dotted circle) amongst distractors of two types: red lines oriented at 45° and green lines oriented at 135° using a button press. The inter-trial interval terminated with the response, or lasted up to a maximum of 4 s. (B) Anatomical location of TMS site. Each circle represents the MNI coordinates identified by the functional localization procedure for each individual participant site at which TMS was applied to the right ANG/IPS in experiments 1 and 2. For illustration purposes, the *y*- and *z*-coordinates for each individual were projected against the group mean *x*-coordinate. The line weight is proportional to the number of participants for which the stimulation coordinates are shown. The stimulation sites cluster around the posterior part of the angular gyrus and inferior border of the intra-parietal sulcus. Coordinate range: $34 < x < 57$, $-75 < y < -47$, $43 < z < 60$. (C) TMS to right ANG/IPS delays reaction time. To illustrate typical mean reaction times on the visual search task, graph shows data for the no TMS versus TMS condition from experiment 1, illustrating the $\geq$20 ms reaction time deficit that was the criterion to identify the right ANG/IPS attention 'hotspot'. (D) Timeline of a single trial of the extinction task used in both experiments. The onset of the central fixation cue onset signaled to participants to monitor both hemifields to detect and report the location of an upcoming transient visual target, which could appear on the left, right or bilaterally, or not at all. This example shows a bilateral target trial. The inter-trial interval (ITI) varied across experiments. (E) Staircase procedure to determine stimulus size for the extinction task. To illustrate the psychophysical thresholding procedure, graph shows the mean percentage accuracy for left, bilateral and right target trials across 5 different stimulus sizes (in arbitrary units, a.u.) from experiment 1. Two adjacent stimulus sizes were chosen per participant based on bilateral trial detection accuracy of 40–60%.

which no TMS was applied. The goal was to identify the scalp location overlying parietal cortex in each individual at which TMS slowed reaction time (> 20 ms delay relative to the preceding no TMS block). Illustrative data are shown in Fig. 1C. TMS was applied iteratively to each of nine points on a 3×3 cm square lattice marked on the scalp and centred over electrode position P4 (i.e.: 9 cm superior from the inion and 6 cm lateral). Points were sampled until the attention 'hotspot' location was found.

The location of the right ANG/IPS hotspot in each individual was then confirmed anatomically using Brainsight frameless stereotaxy (version 1.5 Rogue Research, Canada). Each participant's head was co-registered with their anatomical MRI in native space, and a trajectory was plotted from the TMS 'hotspot' scalp location onto the cortical surface. Individual participants' structural MRI scans were then normalised to the MNI 152-mean brain T1 template. In one individual no attention 'hotspot' location could be found, so TMS was instead targeted at the group mean anatomical 'hotspot' coordinate reported in previous papers using this procedure (i.e.: MNI coordinates $X=41$, $Y=-69$, $Z=43$) (Rushworth et al., 2001). In the current study the group mean ($\pm$SD) coordinates at which TMS was applied were $X=39.60$ (± 8.85), $Y=-61.80$ (± 6.30), $Z=51.80$ (± 6.87) in the behavioural TMS experiment ($n=5$) and $X=41.67$ (± 6.76), $Y=-64.17$ (± 7.87), $Z=48.08$ (± 6.69) in the TMS/fMRI experiment ($n=12$) (Fig. 1B).

2.3. Transcranial magnetic stimulation

Since the main aim of this study was to image the effects of TMS, we chose an offline low-frequency TMS protocol (1 Hz, 15 min) to transiently inhibit the functioning of right ANG/IPS,

similar to Hilgetag et al. (2001). Such offline stimulation protocols have been shown to inhibit neural activity and perturb function for a period that outlasts the stimulation duration by approximately 5–15 min (Boroojerdi et al., 2000; Chen et al., 1997), thus allowing for induced changes in functional brain activity to be detected by subsequent fMRI (O'Shea et al., 2007).

In both the behavioural and TMS/fMRI experiments a biphasic Magstim Super Rapid TMS machine (Magstim Company, Whitland, Wales) was used to deliver 15 min of 1 Hz offline TMS to the right posterior parietal cortex at 90% of resting motor threshold through a 70 mm figure-of-eight coil while participants sat at rest. The coil was held tangential to the skull and oriented at 45° from the mid-sagittal axis over the identified rANG/IPS in each individual. The coil was fixed in place with a metal clamp. To ensure minimal coil movement an experimenter supported both the coil and the participant's head throughout stimulation. Coils were changed after 7.5 min to prevent overheating. Coil changeover took less than 1 min.

Individual resting motor threshold (RMT) was determined at the end of the functional localisation session. The RMT of the right motor cortex was determined for each individual as the minimum intensity of single-pulse TMS to the motor 'hotspot' that induced motor evoked potentials (MEPs) of $\sim$50 μV peak-to-peak amplitude from the first dorsal interosseous muscle of the left hand on an average of 5 out of 10 consecutive trials. TMS to the right ANG/IPS was applied at 90% RMT and 10 additional trials confirmed that this stimulation intensity elicited no MEPs. Electromyographic responses were recorded from silver chloride electrodes in a tendon-belly montage. Responses were amplified, filtered and sampled using a CED 1902 amplifier interconnected with a CED 1401 analogue-to-digital converter (Cambridge Electronic Design Ltd., Cambridge, UK). The signals were recorded using Spike 2 (version 3.21) and Signal (version 2.14) programs. The sampling rate was 5000 samples per second and the signal was band-pass filtered between 10 and 1000 Hz.

2.4. Visual extinction task

In order to test for the behavioural (Experiment 1) and functional (Experiment 2) consequences of offline right ANG/IPS TMS, we used the same target detection task used by Hilgetag et al. (2001) to simulate visual extinction in the healthy brain.

On each trial, participants were required to maintain central fixation and covertly monitor both the left and right hemifield to detect and report the location of transiently presented peripheral visual targets using a button press (Fig. 1D). Each trial began with a central fixation cross (duration randomized between 2 and 4 s) which functioned as a cue, warning the participant that the target stimulus was about to appear. Immediately upon cue offset, the target was presented for 100 ms. A target was either presented in the left visual field ('unilateral left trials'), the right visual field ('unilateral right trials'), or to both hemifields simultaneously ('bilateral trials'). In addition, there were 'catch' trials in which no target was presented. All four trial types were equiprobable. Participants were required to respond on every trial by pressing one of four buttons using the four fingers of their right hand to indicate either 'left', 'right', 'bilateral' or 'none'. Following target offset, a blank screen filled the inter-trial interval (ITI) for a variable duration (jittered between 2 and 4 s in the behavioural TMS Experiment 1; jittered between 6 and 8 s in the TMS/fMRI Experiment 2). Total task duration was approximately 15 min (Experiment 1: 144 trials, Experiment 2: 100 trials).

The targets comprised of small grey squares ($167 \times 167 \times 167$ RGB) presented on a lighter grey background ($170 \times 170 \times 170$ RGB). Following a block of task practice (70 trials, 5 min), participants underwent a psychophysical staircase procedure to determine appropriate threshold-level target sizes for the main task. Five stimulus sizes were tested for each individual, with squares of 8–21 pixels in length across 90 trials. During the thresholding procedure, participants were tested only on unilateral left/right and bilateral trials (chance performance = 33%). Two adjacent target sizes were chosen for each participant based on detection accuracy on bilateral trials of 40–60% (Fig. 1E). After thresholding, participants underwent a second block of task practice in which catch trials were introduced (50 trials, 5 min, chance performance = 25%). In case of a participant's performance failing to exceed chance, target size was adjusted and the block was repeated until criterion was reached. Participants then performed the main task.

During Experiment 1 (behaviour) the task was run on a PC with a Windows 98 operating system (75 Hz refresh rate, 1024×768 resolution) using Presentation software (version 0.52, Psychology Software Tools Inc.). Participants were positioned on a chinrest 44 cm from the screen and targets were presented at 16 cm horizontally and 5 cm vertically from central fixation (ie: at 18° eccentricity). During Experiment 2 (TMS/fMRI) the task was run on a PC with a Windows 98 operating system (60 Hz refresh rate) using Presentation software (version 9.9). Stimuli were back-projected onto a screen in the MRI scanner viewed via a mirror above participants (12.5 cm: distance from mirror to eyes) with targets projected at a viewing angle of 18°. Button presses were collected on a parallel port response box.

2.5. Experimental procedures

2.5.1. Experiment 1: Behavioural effect of right parietal TMS on extinction task

Owing to the anticipated difficulties controlling the visual environment in the MRI scanner, the goal of this prior behavioural experiment was to confirm that the offline right parietal TMS protocol would induce an extinction-like pattern of detection behaviour under psychophysically controlled conditions. To confirm this, participants performed the visual target detection task before and after TMS. Following task practice, participants were dark-adapted for 10 min using a blindfold, after which they underwent psychophysical thresholding to determine the appropriate target sizes, followed by another practice block to confirm the threshold was appropriate. The extinction task was then performed twice, once at baseline (baseline task session) and once after 15 min of 1 Hz TMS (post-TMS task session). TMS was applied to the right ANG/IPS in each individual using Brainsight frameless stereotaxy based on the coordinates derived from the TMS functional localizer procedure performed previously. As it would be necessary for the TMS/fMRI experiment, stimulation order was counterbalanced across the baseline and post-TMS task sessions (2 participants in baseline/post-TMS order, 3 participants in post-TMS/baseline order). For those participants who performed the post-TMS task session first, 45 min elapsed between the end of TMS and the start of the baseline task session. Participants performed 144 trials in each session (36 of each trial type) with an average trial duration of 6.1 s.

2.5.2. Experiment 2: TMS/fMRI of the extinction task

All stimuli, task events and experimental procedures were identical to Experiment 1, except that since the fMRI design was rapid event-related, the inter-trial interval was lengthened (from 2–4 to 6–8 s) to ensure that functional brain activity on trial n could be distinguished effectively from trial $n+1$. Hence, average trial duration was approximately 10.1 s (from 8.1 s to 12.1 s), resulting in 100 trials in total over 15 min. Participants first practiced the task outside the scanner for 5 min (70 trials), followed by a staircase procedure to titrate target size inside the scanner,

followed by the main extinction task during fMRI acquisition. The order of the baseline and post-TMS scan sessions was counterbalanced (6 participants in baseline/post-TMS order, 6 participants in post-TMS/baseline order), both to minimise practice effects and ensure that any changes in brain activity observed after stimulation would not be contaminated by scan order effects. For those participants who performed the post-TMS scan session first, 45 min elapsed between the end of TMS and the start of the baseline scan session. Those participants performed an additional 10 practice trials at the start of the post-TMS scan session, since their first trials might be more error prone. TMS was applied in the console room directly adjacent to the scanner room, and the interval between the end of the TMS train and the start of fMRI data acquisition was approximately 4 min.

2.6. MR image acquisition

Blood oxygenation-level-dependent (BOLD) fMRI images and T1-weighted anatomical images were acquired on a 3T Siemens Trio MR scanner with a maximum gradient strength of 40 mT m^{-1} at the Oxford University Centre for Clinical Magnetic Resonance Imaging (OCMR). Participants wore earplugs throughout TMS and scanning. All participants underwent two scan sessions (baseline scan session and post-TMS scan session) in counterbalanced order. During each session, 620 axial echo-planar volumes (25×6 mm^2 slices, TE = 30 ms, TR = 1500 ms, flip angle = 73°, FOV = 192×192 mm^2, matrix = 192×192, voxel size = $3 \times 3 \times 5$ mm^3) were acquired over 15 min. In addition, a 9-min high resolution structural MRI scan was also obtained (FLASH; repetition time = 3 ms, echo time = 4.71 ms, and flip angle = 80°, giving a voxel size of $1 \times 1 \times 1$ mm^3).

2.7. Functional magnetic resonance imaging data analysis

All image processing and statistical analyses were performed using tools from the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB, Oxford, U.K; www.fmrib.ox.ac.uk/fsl). The first two volumes of each fMRI scan were discarded to allow for T1 equilibration effects. The functional MRI data were then corrected for motion using MCFLIRT (Jenkinson et al., 2002) and non-brain structures were removed using BET (Smith, 2002). The images were spatially smoothed using a 5 mm Gaussian kernel of full-width at half maximum and low-frequency drifts were removed with high-pass temporal filtering with a cut-off period of 100 s. Functional data were registered to participants' structural image and MNI152 standard space by using linear transformation (Jenkinson et al., 2002; Jenkinson and Smith, 2001). fMRI data were denoised using MELODIC (Beckmann and Smith, 2004); components that were related to eye blinks and eye movements were removed.

The time series data were analysed using a general linear model (GLM) approach. Statistical analysis was carried out in FEAT using FILM with local autocorrelation correction (Woolrich et al., 2001). A GLM was performed on a voxelwise basis using a rapid event-related design. The hemodynamic response was modelled as a gamma function, a normalisation of the probability density function of the gamma distribution with zero phase, standard deviation of 3 s, and a mean lag of 6 s.

The major constraint on the fMRI design was the need to complete scanning within a brief period after offline TMS, in order to maximise the chances of detecting a post-stimulation change in brain activity before it would decay. We opted for a 15-min maximum scan period, based on our previous work with a similar offline 1 Hz 15-min TMS protocol (O'Shea et al., 2007). This necessitated a rapid event-related fMRI design, to maximise the number of different trial types and minimise the amount of rest within this 15-min period. As a consequence, trial types were short, and it was not possible to disentangle within-trial components. Specifically, it was not possible to dissociate cue-related from target-related activity. Hence, 4 trial type regressors were constructed that reflected a composite of cue- and target-related activity. Each trial type was modelled using a single explanatory variable (EV) that captured the cue period (jittered between 2 and 4 s) followed by the target (100 ms) on every trial. This yielded 4 distinct EVs that varied with target location: left, right, bilateral, catch (none). The explanatory variables were modeled with their temporal derivatives. Six additional movement parameters were included to capture the remaining head motion-related variance.

FEAT (version 6.00) was used to fit the model to the data, generate parameter estimates for each EV at each voxel, and contrast parameter estimates against the implicit resting baseline. To generate statistical maps of the brain regions specifically engaged in attention and target-related processing (from which motor response-related activity had been subtracted out), we contrasted correct left, right, and bilateral trials versus catch trials.

2.8. Statistical analysis of behavioural data

Accuracy and reaction time data from the extinction task were analysed with repeated measures ANOVA and *t*-tests corrected for multiple comparisons using SPSS software (SPSS inc. version 22.0). Data distribution assumptions of normality were assessed quantitatively using the Shapiro–Wilk test, and qualitatively using Q-Q plots, while sphericity was assessed using Mauchly's test, with violations corrected using the Huyhn–Feldt procedure where appropriate. Responses to the two target sizes were first calculated independently and then averaged for each individual prior to analysis. To specifically test the prediction that right parietal TMS would induce a rightward shift in attentional orienting, relative detection performance between the left and right hemifields was quantified by a lateralization index (LI). LI provides a single numerical value that quantifies participants' relative attentional bias between the left and right hemifields. LI was calculated on hits for unilateral target trials ie: $LI_{unilateral}$ = (right – left hits)/ (right + left hits). For bilateral target trials LI was calculated on errors ie: $LI_{bilateral}$ = ("right"–"left" incorrect responses)/ ("right" + "left" incorrect responses). LI values range between −1 and +1, with 0 indicating no difference between left and right hemifields. Positive LI values indicate a bias towards right space and negative values indicate a bias towards left space. The key prediction was that right parietal TMS would induce an extinction-like behavioural effect on bilateral trials (ie: a relative decrease in the number of incorrect 'left' responses and a concomitant increase in the number of incorrect 'right' responses). That is, we predicted an increase of the bilateral LI (rightward shift) between the baseline and the post-TMS task sessions.

3. Results

3.1. Behavioural data

3.1.1. Experiment 1: Behavioural effect of right parietal TMS on the extinction task

The key prediction was that right ANG/IPS TMS would induce a rightward shift in spatial attention and consequent target detection. Hence, performance on bilateral trials (when participants have to covertly monitor and detect targets in both hemifields) should be the most sensitive measure of any such attentional shift. Specifically, by analogy with clinical extinction, we predicted that TMS would change the spatial distribution of errors on bilateral trials, relatively reducing erroneous 'left' responses while

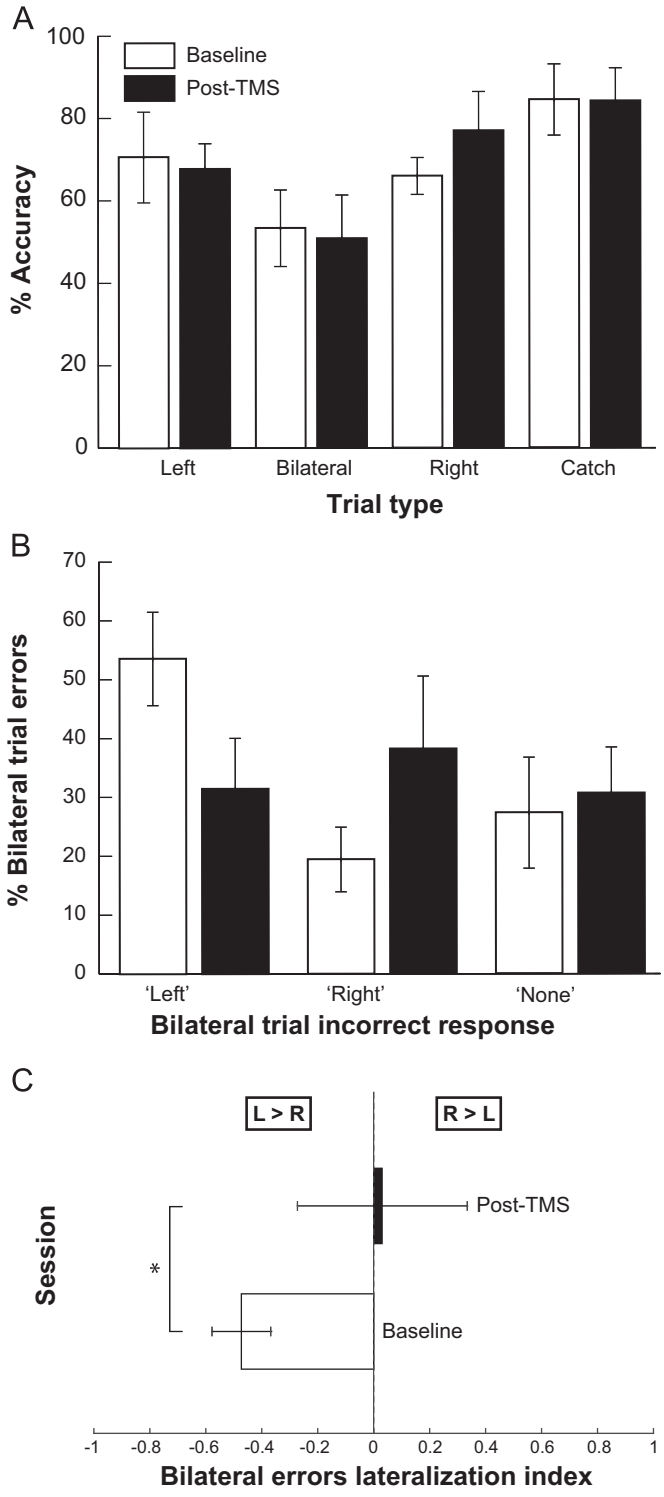

Fig. 2. Behavioural results of Experiments 1. (A) No effect of right parietal TMS on extinction task accuracy. Graph shows percentage correct responses across the four trial types of the extinction task performed outside the scanner. There was no difference in accuracy between the baseline (white) and post-TMS sessions. (B,C) Right parietal TMS shifted the spatial distribution of bilateral trial errors from left to right. (B) Graph shows the relative percentage of incorrect responses ('left', 'right' 'none') on bilateral target trials at baseline (white) and after TMS (black). (C) Graph shows the bilateral Lateralization Index ($LI_{bilateral}$=("right"–"left" incorrect responses)/ ("right"+"left" incorrect responses)) at baseline (white) and after TMS (black). Prior to stimulation, when participants made an error on bilateral trials, they more frequently detected the target on the left than on the right, ie: they showed pseudoneglect. Analysis showed that TMS abolished this bias, relatively shifting the bilateral LI rightward. Asterisk reflects significance level of one sample t-test on the change in LI (delta LI Post TMS – Baseline) against zero (*: $p \leq .05$, one-tail).

increasing erroneous 'right' responses. To assess this, we tested for a change in the direction of error responses on bilateral trials, as quantified by the lateralization index (i.e.: $LI_{bilateral}$=("right"–"left" incorrect responses)/ ("right"+"left" incorrect responses)), after rANG/IPS TMS compared to baseline.

First we tested for the presence of a lateralized spatial bias at baseline (before TMS was applied). A one-sample *t*-test (versus zero) indicated that participants were significantly biased towards the left hemifield at baseline, a well-documented phenomenon known as pseudoneglect ($t(4)= 4.518$, $p=.01$; mean $LI_{bilateral}=-.47$; Fig. 2C). Next we tested the a priori directional prediction that LI values would shift rightward after TMS (ie: increase). A one-sample *t*-test (versus zero) on the change in $LI_{bilateral}$ score (delta Post-TMS – Baseline) confirmed there was a significant rightward shift after TMS ($t(4)= 2.128$, $p=.05$, 1-tailed; mean Δ $LI_{bilateral}=+.503$; Fig. 2). The same analyses on unilateral LI scores were not significant (all $p>.7$). Hence, right parietal TMS induced a highly specific behavioural effect: it shifted participants' baseline spatial bias from left to right, abolishing pseudo-neglect.

Analysis also considered correct target detection ("hit") rates for all three trial types in which a target was present (left, right and bilateral). Repeated-measures ANOVA with factors of TMS (baseline versus post-TMS) and Trial Type revealed a main effect of Trial Type ($F_{(8)}=4.54$, $p=.048$), reflecting the fact that bilateral target trial performance was lower than unilateral trial performance (Fig. 2A). However, there was no effect of TMS ($F_{(4)}=.31$, $p=.61$) and no interaction ($F_{(8)}=.84$, $p=.47$). Analysis of reaction times also confirmed no effect of TMS ($F_{(4)}=.71$, $p=.447$), indicating that the changes observed on bilateral trials were not due to alteration of a speed/accuracy trade-off.

Hence, TMS did not have a generalised non-specific effect on visual sensitivity or response time, but rather had a highly specific effect of changing the spatial distribution of errors on bilateral trials from left to right, thus simulating clinical visual extinction.

3.1.2. *Experiment 2: TMS/fMRI of the extinction task*

The same statistical analyses conducted in Experiment 1 were carried out on the behavioural data in Experiment 2. The overall pattern of detection accuracy in the fMRI experiment was similar to Experiment 1, although baseline hit rates were ~9% higher despite the same mean target size being used, indicating the greater difficulty of titrating performance to psychophysical threshold in the scanner environment (Fig. 3A). As in Experiment 1, TMS had no effect on hit rates, reaction times or unilateral LI scores. By contrast with Experiment 1, there was no evidence of baseline pseudoneglect in the scanner ($p>.11$), and consequently no extinction-like effect of TMS ($p>0.4$).

The absence of a leftward spatial bias ('pseudoneglect') at baseline in the scanner likely reflects the constraints of the visual MRI environment in which accurate psychophysical control over luminance was not possible. Hence, in Experiment 2 it was not possible to investigate neural correlates of, or an effect of TMS on, an absent behavioural effect. However, since behaviour did not differ significantly between the baseline and post-TMS conditions, this meant that any observed changes in fMRI activity could be attributed straightforwardly to a direct causal effect of TMS, without the interpretative complications of concomitant behavioural change.

Hence, whereas Experiment 1 aimed to characterize the causal consequences of TMS for attentional performance under psychophysically controlled visual conditions, the focus of Experiment 2 was physiological, aiming to characterize the causal impact of TMS on functional brain activity mediating attentional performance.

Table 1
Network of brain regions significantly activated by the extinction task. Coordinates are the peak voxel for the contrast [Left/Bilateral/Right–Catch] averaged across the Pre- and Post-TMS scan sessions.

Area	MNI coordinates			*Z* value
	x	*y*	*z*	
Visual cortex				
R	44	−64	−12	4.00
L	−40	−60	−12	3.9
Angular gyrus/intra-parietal sulcus				
R	34	−64	40	3.07
L	−44	−62	50	3.02
Superior parietal lobe				
R	32	−52	62	3.20
L	−28	−56	50	2.95
Precentral gyrus				
L	−32	0	36	2.94

3.2. Functional brain imaging data

3.2.1. Extinction task network

To identify the network of brain regions activated during bilateral attention, independently of any TMS effect, a multi-subject, multi-session mixed effects analysis was conducted. At the first level, Z statistic images were generated for the contrast [Left/Bilateral/Right-Catch trials], separately for the baseline and the post-TMS scan sessions. Then, a second-level fixed-effects analysis was conducted on each participant's pair of scans to yield a Z statistic map reflecting the average pattern of brain activity across both scan sessions. Finally, a third level mixed-effects analysis was conducted at the group level, on the output from the second level analysis per participant, with Z statistic images thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$. All statistical parametric maps are displayed according to radiological convention (i.e.: left and right hemispheres are inverted).

Attentional orienting activated a bilateral network of cortical regions including the angular gyrus/intra-parietal sulcus, superior parietal cortex, visual cortex and left precentral gyrus (Fig. 3B, Table 1). For illustrative purposes, Fig. 3 shows the mean location at which TMS was targeted (1 cm radius sphere shifted one radius inward from the scalp surface stimulation site; MNI coordinates: $x = 36$, $y = -64$, $z = 42$), demonstrating that stimulation was applied to a region of right ANG/IPS that is functionally recruited when participants are covertly monitoring both hemifields in anticipation of an upcoming target.

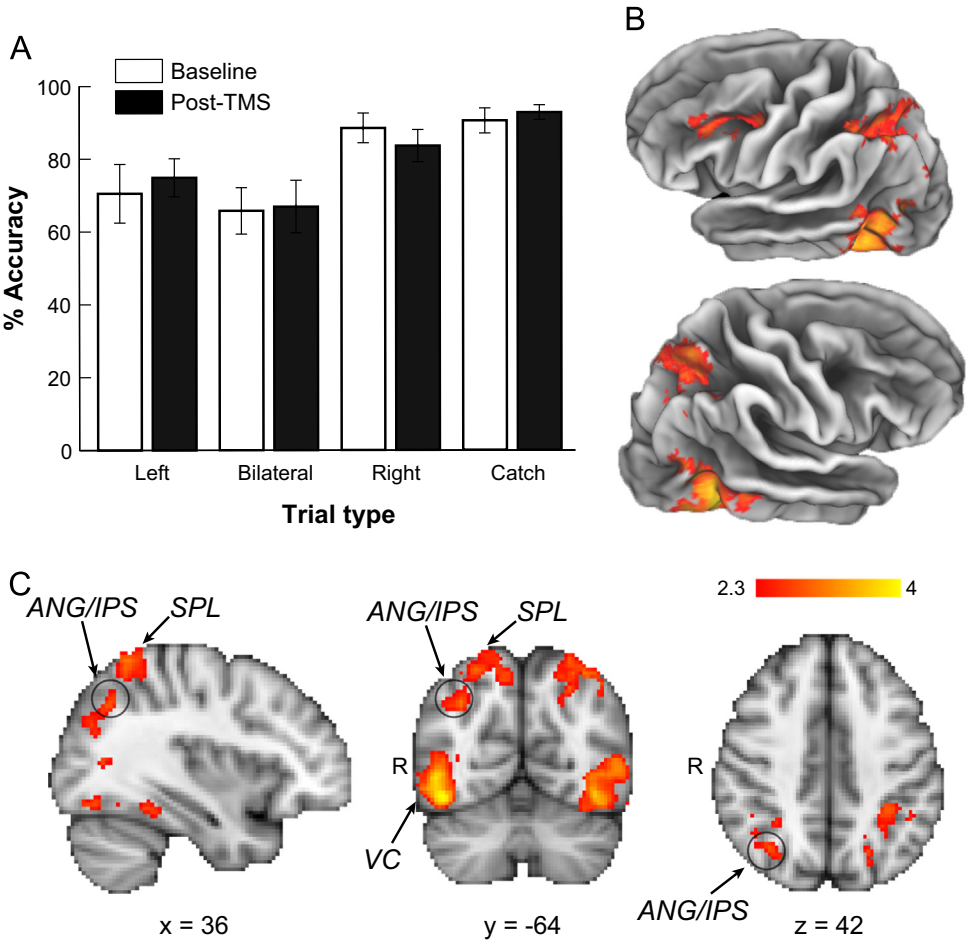

Fig. 3. Cortical network activated during bilateral attention (Experiment 2). (A) No effect of right parietal TMS on extinction task accuracy (experiment 2). Similar to the experiment performed outside the scanner, right parietal TMS had no effect on extinction task performance accuracy during fMRI. (B,C) Figures show regions activated during the extinction task averaged across both the baseline- and post-TMS scan sessions. Performance of the extinction task activated a bilateral network of regions including the angular gyrus/intra-parietal sulcus (ANG/IPS), superior parietal lobe (SPL) and precentral gyrus. Activity is time-locked to cue onset, during which participants were required to covertly monitor both hemifields. Voxelwise statistics represent the contrast [Left/Bilateral/Right – Catch trials] averaged across baseline and post-TMS sessions ($Z > 2.3$, corrected cluster extent significance threshold $p < 0.05$). Colour bar represents Z statistics at each voxel. The black circle illustrates the group mean stimulated MNI coordinate across participants, showing that TMS was applied to the right ANG/IPS, a region normally activated during bilateral attention ($x = 36$, $y = -64$, $z = 42$). The circle was positioned by centering a 1 cm radius sphere one radius distance inward from the mean scalp coordinates along a trajectory perpendicular to the angle of orientation of the TMS coil.

3.2.2. Effect of tms on inter-hemispheric balance

Whole-brain voxel-wise analysis ($Z > 2.3$, corrected cluster significance threshold of $p = 0.05$) revealed no overall increase or decrease in activity anywhere in the brain between the baseline and the post-TMS scan sessions. However, the goal of the study was to test the more specific hypothesis that right ANG/IPS TMS would induce a leftward shift in the *relative balance* of activity between the left and right parietal cortices. The statistical map of the extinction task network computed for the baseline scan suggested there was relatively stronger activity in the right parietal cortex, whereas the same map computed for the post-TMS scan suggested the opposite (Fig 4A). In order to formally assess this, we computed the relative difference in activity between homologous voxels of the two hemispheres for the baseline and the post-TMS scans, and tested for a significant change in functional lateralization caused by TMS. Voxelwise functional lateralization maps were obtained for each scan session using a similar approach to other fMRI studies of functional lateralization (Agcaoglu et al., 2015; Macaluso and Patria, 2007; Shulman et al., 2010). To accurately map homologous voxels across hemispheres, we used a simple left-right flip of the images, followed by a non-linear registration of the (flipped) left hemisphere to the (non-flipped) right hemisphere (Jenkinson et al., 2002). We then generated functional lateralization maps by comparing the non-flipped left hemisphere to the flipped right hemisphere images. For each voxel of the right hemisphere, the lateralization index was calculated as the difference in effect size relative to its contralateral homologous voxel (i.e.: right-left hemisphere) for the contrast [Left/Bilateral/Right-Catch trials]. At the group level, baseline and post-TMS functional lateralization maps were masked to include only grey

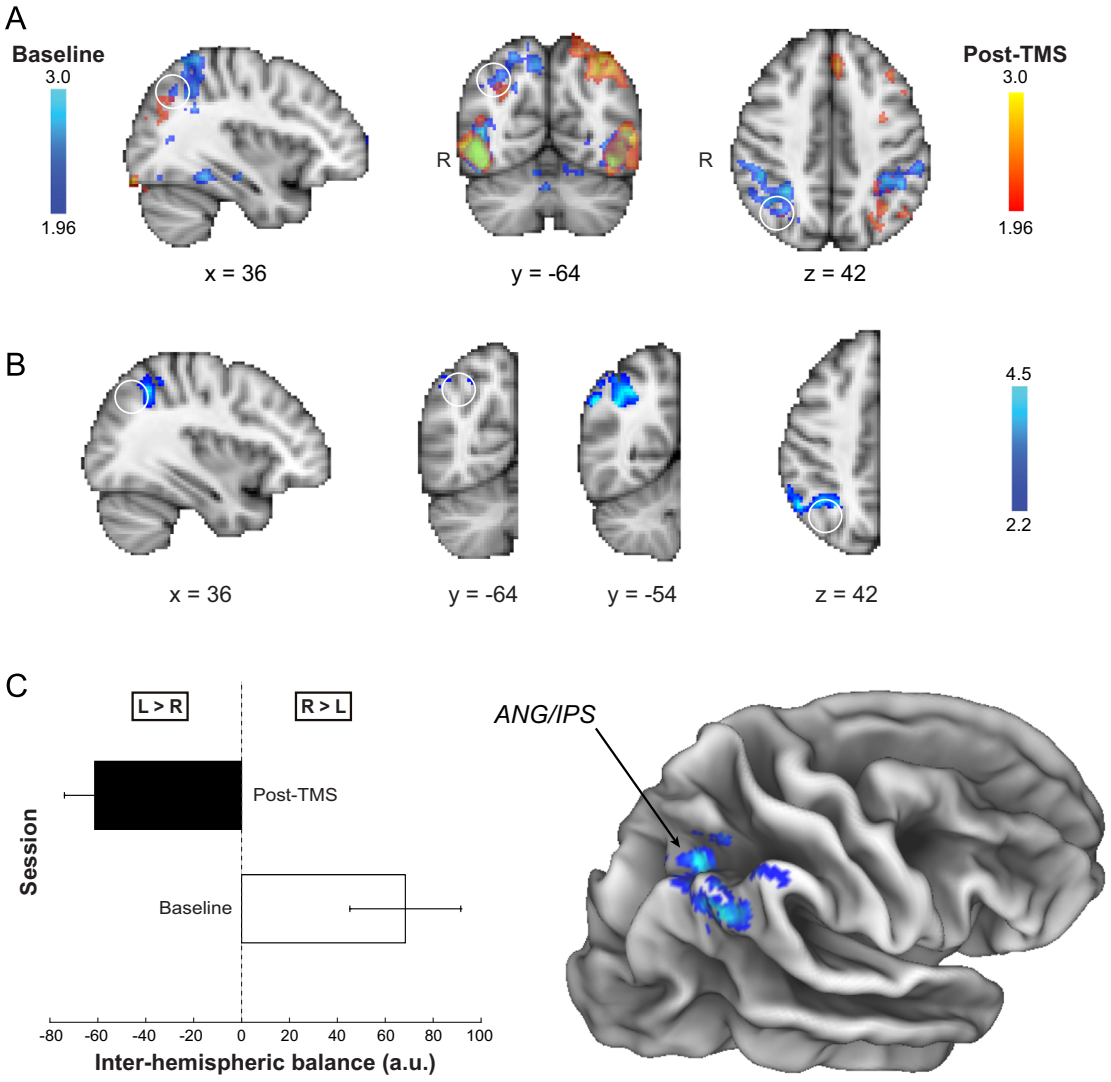

Fig. 4. Effect of TMS on inter-hemispheric balance during bilateral attention. (A) Network activated during bilateral attention before and after TMS. Figure shows regions activated during the extinction task, separately for the baseline (blue) and post-TMS (red) scan sessions. Colour bar represents *Z* statistics at each voxel. Voxelwise statistics represent the contrast [Left/Bilateral/Right – Catch trials] with a voxel height threshold of $Z > 1.96$ and a corrected cluster extent significance threshold of $p < 0.05$. At this threshold, the relative difference in the strength of activity across hemispheres is visible. At baseline there is more supra-threshold activity in the right versus left parietal cortex. Post-TMS this is inverted. (B) Right parietal TMS shifts the inter-hemispheric balance of activity leftward. Voxelwise analysis of functional lateralization within the extinction task network confirmed the apparent difference visible in (A) using a direct and unbiased statistical comparison across the two hemispheres. Homologous voxels were co-registered onto the right hemisphere and compared statistically. Map shows the only region in which there was a significant leftward shift in the relative balance of task activity (right-left hemisphere) after TMS: ANG and the adjacent IPS (stimulated cortex). The white circle illustrates the group mean stimulated MNI coordinate across participants ($x = 36$, $y = -64$, $z = 42$). The circle was positioned by centering a 1cm radius sphere one radius distance inward from the mean scalp coordinates along a trajectory perpendicular to the angle of orientation of the TMS coil. The slice $y = -54$ was added for better visualization of the TMS effect. Colour bar represents *t* statistics at each voxel. (C) Extracted parameter estimates from the region of significant TMS effect. Data extracted from the region of significant TMS effect (as in B) illustrate the inter-hemispheric balance parameter (in arbitrary units, a.u.) from the baseline and post-TMS sessions. R = right hemisphere, L = left hemisphere

matter and were compared using paired sample *t*-tests across participants for each voxel. The resulting statistical maps were thresholded using clusters determined by $t_{(11)} > 2.2$ (corresponding to $p < .025$) and a corrected cluster significance threshold of $p = 0.05$.

Right ANG/IPS TMS caused a significant leftward shift in hemispheric balance (functional lateralization) that was confined to the stimulated angular gyrus and adjacent intraparietal sulcus (peak voxel: $X = 54$, $Y = -54$, $Z = 40$, $t(11) = 6.14$, $p < 10^{-4}$; Fig. 4B, C). No brain region showed a rightward shift in hemispheric balance after TMS.

4. Discussion

This study aimed to test a hypothesis generated from theoretical models of the pathophysiology of visual extinction and neglect: that bilateral attentional function in the healthy brain depends causally on the balance of functional activity between left and right parietal cortex (Cohen et al., 1994; Kinsbourne, 1977). To test this, participants performed a target detection task in which they were required to maintain central fixation while covertly monitoring both hemifields simultaneously to detect and report the location of an upcoming target stimulus. Low-frequency TMS was applied to transiently inhibit the right ANG/IPS. Experiment 1 assessed the behavioural effects of this stimulation protocol under psychophysically controlled conditions. Analysis of errors on bilateral trials revealed that, prior to TMS, participants exhibited an attentional bias towards the left hemifield (pseudoneglect) (Fig. 2B). TMS shifted the spatial distribution of errors from left to right, simulating visual extinction and abolishing pseudoneglect. Experiment 2 then assessed the effect of TMS on functional brain activity during bilateral attention. TMS did not cause an overall increase or decrease in activity anywhere in the brain. Rather, TMS shifted the *relative balance* of inter-hemispheric activity from right to left, an effect that was confined to parietal cortex. In combination, across the two experiments, the coherent direction of change in the TMS-induced behavioural (left-to-right) and functional (right-to-left) effects supports the hypothesis that bilateral spatial attention causally depends on parietal inter-hemispheric balance.

4.1. Behavioural effect of right parietal TMS on the extinction task

Given the inability to obtain precise psychophysical control over visual stimuli within the scanner, a behavioural experiment was first conducted outside the scanner in a subset of participants to confirm that stimulation of the right ANG/IPS would induce an extinction-like behavioural effect (for similar logic in an online TMS/fMRI study see Ruff, et al., 2006). The same visual target detection task was used as in the subsequent fMRI experiment, except that the task in the laboratory was better sensitised to detect a behavioural effect of TMS. Trial pacing was faster (mean ITI of 3 versus 7 s), requiring participants to perform a larger number of trials within the same 15 min time period (144 versus 100), and there was no delay between the offset of TMS and the onset of task performance. Critically, visual luminance could be precisely controlled, ensuring that the staircase procedure more accurately estimated participant's psychophysical detection threshold. Under these conditions, TMS induced a subtle but measurable behavioural effect. Analysis of the spatial distribution of errors on bilateral trials showed that at baseline, prior to stimulation, participants exhibited an attentional bias towards the left hemifield, a phenomenon known as pseudoneglect. Pseudoneglect is a leftward bias in spatial attention reliably observed in healthy individuals across a range of tasks (Bowers and Heilman, 1980; Jewell and McCourt, 2000; Mattingley et al., 2004; Nicholls et al., 1999). Taken together with the higher prevalence of spatial neglect after right than left hemisphere lesions, the phenomenon of pseudoneglect in healthy individuals is thought to reflect right hemisphere dominance (or even lateralization) of some visual attention processes in the general population (Benwell et al., 2014; Cicek et al., 2009; Le et al., 2015). After stimulation, pseudoneglect was abolished with participants now tending to report a target on the right and omitting the target on left (Fig. 2B), simulating clinical visual extinction. Thus the behavioural TMS experiment established that right ANG/IPS has a causal role in bilateral attention, replicating previous work (Hilgetag et al., 2001).

4.2. Effect of right parietal TMS on functional brain activity during bilateral attention

Previous behavioural TMS studies had reported that stimulation of right inferior parietal cortex could induce extinction-like behaviour, which was presumed to reflect TMS-induced changes in the balance of functional activity between left and right parietal cortex (Dambeck et al., 2006; Hilgetag et al., 2001; Meister et al., 2006; Pascual-Leone et al., 1994). The present study was designed to test this hypothesis directly, by imaging the causal impact of stimulation on bilateral attention networks using whole-brain fMRI. The extinction task activated an expected bilateral network of parietal, frontal and visual cortical areas (Fig. 3, Table 1), including the region of right ANG/IPS that was the target for TMS. Whole-brain voxelwise analysis showed that stimulation did not cause an overall increase or decrease in activity. Rather, stimulation shifted the *relative balance* of activity between the right and left hemisphere, inducing a relative leftward shift selectively in the ANG/IPS while participants were covertly monitoring both hemifields (Fig. 4B). An advantage of this analysis approach is that it tests directly the central claim of the original inter-hemispheric rivalry model – that it is the *relative* balance between (and not the overall level of activity within) left and right parietal cortex that determines the spatial allocation of attention (Kinsbourne, 1977). The counterbalanced order of baseline and post-TMS scan sessions rules out alternative artefactual explanations of this effect, such as non-specific changes in arousal after TMS, task learning across scan sessions, or fatigue from increasing time-on-task.

A key feature of the target detection task was that, on every trial, participants were required to monitor both hemifields simultaneously in anticipation of an upcoming target. Thus, every trial started with a cue period (2–4 s) that required bilateral spatial attention. Whilst the rapid event-related fMRI design did not allow for cue- and target-related periods to be dissociated from one another within a trial, two aspects of the results suggest that stimulation most likely affected this bilaterally-directed cue-period activity, rather than subsequent target-related processing. First, stimulation changed the pattern of brain activity similarly across all trial types (right, left, bilateral), consistent with a similar function being disrupted on all trials (Suppl. Fig. 1). Second, examination of the time course of fMRI signal change within the region of TMS effect (Suppl. Fig. 2) clearly shows a change in inter-hemispheric balance when the data are aligned at cue onset; no signal difference is observed when the same data are aligned on target onset (data not shown). Hence, the fMRI data suggest that right parietal interference (with TMS, but possibly also in the case of a lesion) likely induces a rightward bias in top-down preparatory spatial attention signals, rather than altering target-related processing, as might alternatively account for extinction. The behavioural cost of such an induced rightward functional bias is likely to be most readily apparent on bilateral target trials, as these are the most attentionally demanding and therefore the most behaviourally sensitive.

4.3. No baseline behavioural effect ('pseudoneglect') in the scanner

By contrast with the leftward spatial bias observed at baseline in Experiment 1 (and subsequently abolished by TMS), no such pseudoneglect was present in the fMRI study.

The visual environment in the MRI scanner precluded precise psychophysical control over luminance parameters, and hence the perceptibility of stimuli. Hence, it was not possible to titrate stimuli to psychophysical threshold inside the scanner with the same precision as outside the scanner, meaning that the fMRI experiment was necessarily less sensitive to subtle behavioural change. This was already clear at the pilot stage. The fact that the same mean stimulus size was used in both experiments (ie: 12 pixels), but performance was on average ~9% higher at baseline in the fMRI study (compare Figs. 2A and 3A) testifies to this. We believe that the absence of baseline pseudoneglect inside the scanner, despite its presence outside the scanner in a subset of the same participants, reflects this reduced measurement sensitivity. In addition, the rapid event-related design required a relatively long inter-trial interval (6–8 s). This, combined with the need to complete scanning within 15 min (to maximise the likely window of decaying TMS effect), entailed fewer trials in the scanner. This reduced power compared to the equivalent behavioural experiment outside the scanner (reduction from 144 to 100 trials). More importantly, slowing the pace of task performance made the task less demanding, further reducing behavioural sensitivity. Hence, in summary, the fMRI experiment was optimised to detect the physiological impact of TMS on the bilateral attention network, but not its behavioural consequences.

4.4. No effect of TMS on behaviour in the scanner

The absence of pseudoneglect in the scanner environment meant there was no baseline behavioural phenomenon for TMS to change. Hence, unlike in Experiment 1, TMS in the scanner had no measurable effect on extinction task performance. One benefit of this is that it enabled us to attribute any observed changes in functional brain activity to a direct causal effect of TMS, without any contamination by behavioural change. The absence of a behavioural effect in the scanner does, however, raise the question of the functional significance of the observed TMS-induced change in inter-hemispheric balance. There are at least three possible interpretations: (1) the changes are epiphenomenal; (2) they reflect a compensatory response to stimulation; or (3) they reflect neural changes likely to cause extinction-like behaviour if measured under psychophysically controlled conditions. We think the observed changes are unlikely to be epiphenomenal. The fMRI effect cannot be explained as a simple *passive* consequence of the removal of transcallosal inhibition, whereby inhibitory stimulation to right ANG/IPS would cause an automatic increase in excitation in left parietal cortex. Such an effect, if present, would be common to both the implicit resting baseline and task-related periods, and since fMRI contrasts subtract across these conditions, this would cancel out and hence not be detectable. Consequently, the change in inter-hemispheric balance indicates that TMS modulated the *functioning* of right ANG/IPS, rather than simply changing cortical excitability and leaving function unaffected. The second possibility is that the changes reflect compensation in response to TMS-induced functional interference. We cannot rule this out. Note the necessary delay in the TMS/fMRI experiment between the end of stimulation and the onset of MRI data acquisition (~4 min). Any behavioural interference effects of offline TMS are likely to be strongest in this immediate post-stimulation period, before the system has had much time to recover. In this period behaviour could not be measured. The combination of this 4-min delay, together with an offline stimulation protocol, may have provided sufficient opportunity for the brain to compensate sufficiently for the stimulation so as to maintain task performance despite neural activation change (see for example O'Shea et al., 2007). However, given that Experiment 1 showed no effect of TMS on any task measure other than pseudoneglect, and given that pseudoneglect was already absent during the baseline scan, we do not think a 'compensatory' account makes explanatory sense. Our preferred, parsimonious interpretation is that the coherent direction of TMS-induced behavioural change (rightward shift) in Experiment 1, and functional change (leftward shift) in Experiment 2, is consistent with inter-hemispheric competition models of visual extinction (Kinsbourne, 1977; Szczepanski and Kastner, 2013; Szczepanski et al., 2010). Hence, we speculate that the TMS-induced changes in brain activity observed in Experiment 2 are likely to causally underwrite the TMS-induced behavioural effect observed in Experiment 1, but the latter requires psychophysically controlled measurement conditions to be detectable. In brief, we speculate that these TMS-induced neural changes may be causally necessary to induce an extinction-like behavioural change, but they are not sufficient.

5. Conclusions

The present study is the first, to our knowledge, to directly test the inter-hemispheric balance model of visual extinction in the healthy brain, using a task similar in kind to that used in the clinic. Whilst the behavioural and functional effects of TMS were observed in two separate experiments, the direction of TMS-induced change was consistent across the two studies (i.e.: leftward shift in brain activity, rightward shift in behaviour), and occurred in individuals who had participated in both experiments. Hence, we speculate that the TMS-induced change in inter-hemispheric balance observed here is likely, under behaviourally demanding and psychophysically controlled conditions, to induce extinction-like behavioural interference, similar to that observed outside the scanner. Hence, these results support the claim of theoretical models that bilateral attention in the healthy brain depends critically on the balance of functional brain activity between left and right parietal cortex.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2015.04.021.

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