Neuropsychologia 47 (2009) 3152–3161

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Novel 'hunting' method using transcranial magnetic stimulation over parietal cortex disrupts visuospatial sensitivity in relation to motor thresholds

R. Oliver[a,*], O. Bjoertomt[b], J. Driver[b], R. Greenwood[c], J. Rothwell[a]

[a] Sobell Department of Motor Neuroscience, UCL Institute of Neurology, University College London, 33 Queen Square, London WC1N 3BG, UK
[b] UCL Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK
[c] The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

ARTICLE INFO

Article history:
Received 27 November 2008
Received in revised form 19 July 2009
Accepted 24 July 2009
Available online 3 August 2009

Keywords:
Transcranial magnetic stimulation
Perception
Attention
Parietal cortex
Motor threshold

ABSTRACT

There is considerable inter-study and inter-individual variation in the scalp location of parietal sites where transcranial magnetic stimulation (TMS) may modulate visuospatial behaviours (e.g. see Ryan, Bonilha, & Jackson, 2006); and no clear consensus on methods for identifying such sites. Here we introduce a novel TMS "hunting paradigm" that allows rapid, reliable identification of a site over the right anterior intraparietal sulcus (IPS), where short trains (at 10 Hz for 0.5 s) of TMS disrupt performance of a visuospatial task. The task involves detection of a small peripheral gap (at 14° eccentricity), on one or other (known) side of an extended (29°) horizontal line centred on fixation. Signal-detection analysis confirmed that TMS at the right IPS site reduced sensitivity (d') for gap targets in the left visual hemifield. A further experiment showed that the same right-parietal TMS increased sensitivity instead for gaps in the right hemifield. Comparing TMS across a grid of scalp locations around the identified 'hotspot' confirmed the spatial-specificity of the effective site. Assessment of the TMS intensity required to produce the phenomena found this was linearly related to individuals' resting motor TMS threshold over hand M1. Our approach provides a systematic new way to identify an effective site and intensity in individuals, at which TMS over right-parietal cortex reliably changes visuospatial sensitivity.

1. Introduction

Previous work has shown that transcranial magnetic stimulation (TMS) can alter performance in some visuospatial tasks when delivered over posterior parietal (PPC) sites; for instance, producing a rightward bias in line bisection or landmark-based tasks (e.g. Fecteau, Pascual-Leone, & Théoret, 2006; Fierro et al., 2000, 2006; Muggleton, Cowey, & Walsh, 2008; Pourtois, Vandermeeren, Olivier, & de Gelder, 2001; Valero-Cabré, Rushmore, & Payne, 2006). The effects may be lateralised (with right-parietal TMS typically more effective) and may also interact with the visual field tested. For example, numerous studies using right-parietal TMS in healthy subjects reveal disruption of visual performance in the contralateral left visual hemifield (e.g. Dambeck et al., 2006; Jin & Hilgetag, 2008; Koch, Oliveri, Torriero, & Caltagirone, 2005; Meister et al., 2006; Muggleton et al., 2006; Pascual-Leone et al., 1994) and/or enhancement instead for the right hemifield (see Fecteau et al., 2006 for a detailed review). Right-parietal TMS can also produce enhanced ipsilateral somatosensory sensitivity (Blankenburg et al., 2008; Seyal, Ro, & Rafal, 1995). In one prominent visual example, Hilgetag, Théoret, and Pascual-Leone (2001) reported that extended 1 Hz repetitive TMS over right-parietal PPC led not only to subsequent contralateral impairment, but also to ipsilateral enhancement of visual target detection. Chambers, Stokes, Janko, and Mattingley (2006) reported that short (0.5 s) bursts of right PPC TMS at 10 Hz may selectively enhance the localisation of ipsilateral targets in bilateral visual arrays.

Clinically, TMS has been used to explore possible therapeutic effects of TMS or repetitive TMS in patients with spatial neglect after unilateral brain injury, when applied over the undamaged hemisphere. The notion of 'interhemispheric rivalry' (Kinsbourne, 1977) suggests that the undamaged hemisphere may become hyperexcitable in neglect, and hence that applying TMS to that hemisphere might potentially rebalance or normalise this (see Koch et al., 2008, for a more extended overview). Single or short trains (up to 5 TMS pulses at 20 Hz) of left parietal or frontal TMS have been reported to reduce contralateral extinction for tactile stimuli in unilateral right-hemisphere stroke patients (Oliveri, Rossini, Traversa, et al., 1999). Moreover, 1 Hz stimulation over the unaffected hemisphere may ameliorate a rightward bias in pre-transected line judgements for up to 15 days (Brighina et al., 2003), and cause some improvement in the perception of chimeric figures (Koch et al., 2008) in neglect patients.

* Corresponding author at: 3rd Floor, 33 Queen Square, London WC1N 3BG, United Kingdom. Fax: +44 020 7278 9836.
E-mail addresses: r.oliver@ion.ucl.ac.uk, roliver25@hotmail.com (R. Oliver).

0028-3932/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2009.07.017

In all of the PPC studies above, TMS was applied over a parietal target defined either with MRI-based frameless stereotaxy (which is not always practical, as in some clinical patient studies); or by simply targeting a point (P3, P4, P5, or P6) defined by the 10/20 EEG electrode placement system. However, neuroimaging studies indicate that the anatomical network underlying visuospatial attention in normals may be rather widely distributed (e.g. see Corbetta & Shulman, 2002; Mort et al., 2003). Moreover, at the level of each individual subject or patient, it can be unclear exactly which site of potential parietal TMS stimulation should produce the greatest impact on visuospatial function (see Ryan, Bonilha, & Jackson, 2006). Recent TMS work in normals has shown that merely using the scalp coordinates of conventional EEG electrode-sites can be rather ineffective (Sack et al., 2009). Moreover, for electrode sites such as P3 and P4, the anatomical structures underlying them have been shown to vary rather substantially between individuals. For instance, the two structures most likely to underlie P4 are not only the right angular gyrus (~63% of the time), but also the right superior occipital gyrus (~22% of the time), according to Okamoto et al. (2004).

Using a target site that is defined functionally within each subject, rather than anatomically, might enhance systematic impacts on visuospatial processing, thereby speeding progress both in understanding these effects and in seeking to exploit them clinically. One solution is a 'hunting procedure', whereby the effect of TMS on a visuospatial task is assessed briefly over a number of different sites, and the optimal site as defined functionally (in terms of behavioural impact) is then selected as the TMS target for more detailed testing, with the same and/or other visuospatial tasks. For example, according to one influential proposal (Ashbridge, Walsh, & Cowey, 1997), a 3×3 grid can be drawn around P3 or P4 and the best TMS site to disrupt visuospatial search may then be found by comparing the effects for 16 trials at each site. The 'hotspot' in this particular protocol has been defined as the point where TMS increases subjects' reaction time by 100 ms or more (Ashbridge et al., 1997). Subsequent TMS over such a pre-defined point was shown to cause a contralateral deficit in line-judgement tasks but no lateralised deficit in visual search tasks, hinting at some possible mismatch between the hunting procedure and quent experimental findings (Ashbridge et al., 1997; see also Ellison, Schindler, Pattison, & Milner, 2004).

Although influential, the particular hunting procedure of Ashbridge et al. (1997) is time-consuming, and moreover it relies on reaction-time effects that might not necessarily reflect genuine changes in visuospatial sensitivity or '*d*-prime' (d'). The aim of the present study was to develop a modified hunting procedure for right-parietal TMS effects upon visuospatial performance, in a task which is well suited for application of signal-detection theory to allow sensitivity measures such as d'. We describe a rapid and simple method of localising an effective TMS site over right-parietal cortex, which provides an alternative or supplement to the established techniques mentioned above. We go on to validate this new protocol in a subsequent series of experiments, which show that it is both reliable and specific.

In the first set of studies below we describe the new procedure, test its reproducibility, and identify the most effective right-parietal site. In the second and third sets of studies, we use signal-detection analysis to examine our findings in detail, to confirm a genuine effect on perceptual sensitivity, and to verify that the induced visuospatial effects differ between contralateral and ipsilateral visual hemifields (in fact inducing opposite effects for the two hemifields during right-parietal TMS). Finally, we explore the TMS intensity needed to disrupt visuospatial sensitivity and whether this can be predicted from an individual subject's resting motor threshold. If so, this would then allow the TMS intensity for visuospatial experiments to be readily adjusted to match each individual subject, along with an individual parietal TMS-site location as identified via our new hunting procedure.

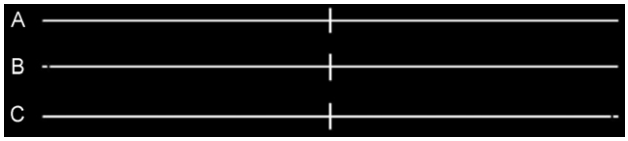

Fig. 1. Illustrations of the 3 different stimulus types used: (A) 'No Gap', (B) 'Left Gap', and (C) 'Right Gap' (Stimulus C was used in Experiment 3 only, and that experiment did not include Stimulus B; hence, within any one experiment, subjects always knew in advance where the gap might appear, if present). Stimuli were presented using the '*E*-prime' software package (Psychology Software Tools Inc., Pittsburgh). In all experiments the stimuli comprised white lines on a black background, bisected with a vertical marker that corresponded to the middle of the preceding fixation cross. The lines (Fig. 1) occupied 29.36° of visual angle (26.2 cm long at a distance of 50 cm) with any gap if present being 1.5 mm (0.17°) wide, situated 2 mm from the left or right end of the line (eccentricity of 14.31–14.47° from the midline).

2. General methods

The study was approved by the local ethics committee. Subjects gave written informed consent and were all healthy volunteers with normal or corrected vision by self-report (see individual experimental procedures for detailed information on handedness, age and gender).

In all experiments, subjects sat with head and chin stabilised in a frame at 50 cm from a PC laptop screen (refresh rate 50 Hz). We used a laptop because the ultimate aim of our study was to introduce a new protocol that would be suitable for clinical TMS studies in a hospital or bedside setting. The visual stimuli used are shown in Fig. 1, and each comprised a long horizontal line (extending 29° of visual angle), with a small vertical mark at its centre to indicate the central fixation point. The task was to detect the presence (as in Fig. 1B or C) or absence (as in Fig. 1A) of a small gap, which could appear near the far left (Fig. 1B) or far right (Fig. 1C) of each line when present, at 14° of eccentricity. Unlike the well-known line-bisection task, our gap-detection task is unambiguous regarding which visual hemifield is most relevant for a particular detection judgement. This is because the gap (when present) was either at the far-left (Experiments 1, 2 and 4) or far-right (Experiment 3), but was never present on both sides concurrently. This contrasts with the horizontal extents that are compared between sides during the line-bisection task, or standard variants upon that task such as judgements of prebisected lines. Moreover, in all our experiments the subjects were instructed regarding which side (far-left or far-right) the gap could appear on with this remaining constant throughout each experiment. They nevertheless had to maintain central fixation, as we confirmed with eye-tracking. The foreknown nature of the task-relevant location where the gap might appear contrasts with other paradigms involving potential search of either or both sides, and should minimize any strategies that trade-off different locations.

Visual stimulus duration was tailored for each subject to achieve a % correct rate of ~95%, using a 'staircase' procedure as described in detail below. TMS was delivered over right-parietal cortex using a Magstim Super Rapid stimulator (Magstim, Whitland, UK). A figure-of-eight coil with diameter 70 mm delivered 5 biphasic pulses at 10 Hz, starting 100 ms before visual display onset and ending with the final pulse being delivered 400 ms after initial visual display onset. These TMS bursts were chosen on the basis of previous studies where 5 pulses at 10 Hz led to reported 'neglect-like' (visuospatial) deficits in line bisection tasks, when given over the right PPC (Bjoertomt, Cowey, & Walsh, 2002; Ellison et al., 2004). By starting the train of pulses 100 ms before visual stimulus onset we hoped to disrupt subjects' covert monitoring of the gap target's future

location thereby maximising any effect of the subsequent TMS pulses. The initial TMS intensity used was 100% of the subject's resting motor threshold (RMT), apart from in our final experiment for which TMS intensity was varied. As in other studies in which visual or tactile perception has been affected with TMS over parietal cortex, the coil was held with the handle pointing backwards so as to induce a current with initial phase flowing in the posterior–anterior direction in the underlying brain (see Koch et al., 2005; Oliveri, Caltagirone, et al., 2000; Oliveri, Rossini, et al., 2000). RMT was determined to the nearest 1% of maximum stimulator output, and defined as the minimal stimulus intensity required to produce a Motor Evoked Potential (MEP) of more than 100 μV in at least 5 of 10 consecutive trials (see Rossini et al., 1994).

2.1. Experiment 1: procedure

Following a fixation cross, 9 subjects (8 male and 1 female aged 25–36, Edinburgh Handedness inventory score (mean ± SE) of 84 ± 10) were shown on each trial either an unbroken horizontal line (Fig. 1A) or a line with a 'gap' at the far left (Fig. 1B), equiprobably. They were instructed to keep their eyes fixed on the centre of the screen (as confirmed later with eye-tracking) and to indicate their perception ('gap' or 'no gap') with a key press. Note that the gap, when present, could only appear on the far left in this particular experiment, as was known to the subjects. For each subject, a suitable presentation duration (PD) was determined (in the absence of TMS) with a staircase procedure, aiming for 95% of the stimuli being correctly identified as containing a gap or no-gap. Using single blocks of 20 trials, the PD was adjusted in 20 ms steps starting at 80 ms. If performance for one block was lower or higher than the desired 1/20 error rate, the PD was adjusted one step up or down, respectively. The staircase ended if the desired error rate was attained, with the last PD then being deemed suitable. Alternatively, if a reversal in performance occurred around the desired error rate, a retest was administered using the shorter PD of the preceding two blocks. The shorter or longer PD of these two blocks was deemed suitable if the retest error rate was below or above (respectively) the desired rate. For all subjects, the selected PD was typically 20–40 ms (mode of 20 ms, mean of 29 ms).

During the TMS hunting procedure itself, the left 'gap' was in fact presented more often (now 90% of trials, unknown to the naïve subjects), but as explained below was often missed nevertheless due to the TMS. We decided to keep the hunting procedure for identifying a hotspot as simple as possible initially, basing it only on 'misses' and 'hits' (though full signal-detection measures that incorporate 'false alarm' and 'correct rejection' rates were used in subsequent cross-validation experiments). For this reason the proportion of 'no gap' trials (which yield neither 'misses' nor 'hits' and thus did not contribute to initial localisation of the 'hotspot') was kept low at 10% during the hunting procedure. Once the subject was able to correctly identify 4 consecutive 'gap' stimuli (as a final confirmation of good performance), TMS was delivered during stimulus presentation as described above (i.e. 5 TMS pulses at 10 Hz and 100% RMT, beginning 100 ms prior to display onset).

The coil position at the start of the experiment was EEG 10–20 position P4 in all subjects. This location was selected on the basis of previous TMS studies (Dambeck et al., 2006; Hilgetag et al., 2001; Jin & Hilgetag, 2008; Koch et al., 2005; Oliveri, Caltagirone, et al., 2000; Oliveri, Rossini, et al., 2000; Pascual-Leone et al., 1994; Pourtois et al., 2001) in which reliable effects on spatial judgments were found using P4 as the target TMS site. Those past studies suggest that a procedure hunting for a particularly effective parietal-TMS site (as here) should meet with success relatively fast if sites near P4 are sampled initially. Starting at P4, the coil was moved along a spiral-shaped path using a 'miss-stay', 'hit-shift' protocol, until a site was reached where the subject missed four consecutive gaps. Hence a TMS site was judged as effective when subjects demonstrated a rise in the 'miss-rate' for left gaps as compared to the 4/4 hits scored just before the start of the TMS.

With our hunting procedure, we aimed to sample a relatively large number of points in a short space of time, rejecting those points unlikely to provide a true 'hotspot' as quickly as possible (hence the low proportion of 'no-gap' trials), while at the same time maintaining a low risk of declaring a false hotspot. A spiral-shaped path gives a particularly effective spatial coverage of a sampling surface in a time-efficient manner, a property exploited in techniques as diverse as MRI (see Sykora, 2005, their Fig. 6) or the production of machine tools (see Wieczorowski, 2001). The coil was moved from P4 in 0.5 cm steps along a path which approximated a clockwise spiral drawn through the intersections of a grid (e.g. lateral, posterior, medial, medial, anterior, anterior, lateral, lateral, lateral, posterior and so on). Accuracy was improved by first marking out a grid for the experimenter's visual reference, centred on the point formed by the coil's anterior concavity, given that the coil's initial centre lay over P4 (a grid centred over P4 would hence have been obscured by the coil for most of the hunting procedure). To prevent a sampling-bias towards those points postero-lateral (or antero-medial) to P4, the first movement of the coil alternated across subjects between medial or lateral (with the overall spiral shifts still clockwise). Even this counterbalancing of first shift leaves some potential for sampling 'bias', in the sense of anterior–lateral and posterior–medial points being sampled somewhat later, but as we show later in Section 3, any such residual sampling-bias was in practice very small) The spatial resolution of typical TMS coils has been quoted as approximately 1 cm^2 (e.g. Walsh, 1998), though sites established as empirically distinguishable on the basis of TMS effects range from 0.5 cm apart (as over motor cortex, Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992) through to 0.5–1.5 cm apart (as over occipital cortex, O'Shea & Walsh, 2007, or over visual association areas, Beckers & Hömberg, 1992; Pascual-Leone, Bartres-Faz, & Keenan,1999). By moving the coil in steps of 0.5 cm here, we could therefore be confident that a functionally distinct location such as the 'hotspot' should not be missed.

In each individual subject the scalp location of the coil at the end of the hunting procedure, hereafter termed the (parietal) 'hotspot', was recorded relative to the EEG '10/20' position P4. In addition, this point was recorded using an infra-red positioning system (Northern Digital, Waterloo, Canada), and the Brainsight Frameless software package (Rogue Research, Montreal, Canada). The separate motor TMS hotspot was defined as the optimal site for eliciting MEPs in the left FDI muscle, and was likewise marked on the subject's structural MRI scan. In a follow-up study the right-parietal hotspot was again determined initially by the hunting procedure as before. This time, however, subjects continued with the 'left gap'/'no gap' discrimination task for 20 more trials (still with 90% of trials actually containing 'left gaps' during TMS), now while wearing an IRIS Skalar Infra-red Eye Tracker. This was to confirm that any reduction in perception of gaps at the far-left of the horizontal line during right-parietal TMS over the hotspot could not be due to substantial TMS-induced deviations of the eyes towards the right.

2.2. Experiment 1 results: reproducibility of the hunting procedure

In all 9 subjects the hunting procedure yielded a point over right-parietal cortex where TMS led to increased misses for left gaps, on average taking 62 ± 7 trials to find. The average site across all 9 subjects was 2.2 ± 0.3 cm (mean ± SE) anterior and 1.3 ± 0.3 cm medial to the P4 '10/20' EEG site. In all subjects the site was mapped onto each individual's structural MRI scan using neuronavigation (see Fig. 2). This corresponded to a point along the anterior intraparietal

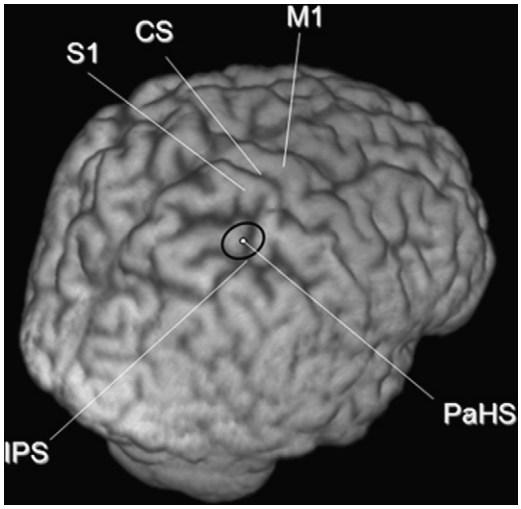

Fig. 2. The position of the 'Parietal Hotspot' (PaHS) averaged over 9 subjects' structural MR scans. CS = Central Sulcus, M1 = Primary Motor Cortex, S1 = Primary Somatosensory Cortex, IPS = Intra Parietal Sulcus, PaHS = 'Parietal Hot Spot'. The coordinates of the coil location at the end of the hunting procedure (see main text) as reported in MNI space (ICBM152 template) and using the Talairach stereotaxic convention (Talairach & Tournoux, 1988), were averaged. The coordinates were transformed using the FLIRT programme (FSL 3.2 package, fMRIB, University of Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/) from native space to normalised structural image space. The black ellipse represents the 95% confidence limits. Note that the long axis of the ellipse lies in the same direction as the TMS coil handle and short axis of the coil, along which the induced magnetic field is more variable. The narrower axis of the ellipse lies along the long axis of the figure of 8 coil where the magnetic field induced is less variable. This may explain the elliptical shape of the 95% confidence limits on site location shown.

sulcus, just posterior to its junction with primary somatosensory cortex (mean Montreal Neurological Institute coordinates of $X = 42.3$, $Y = -50.3$, $Z = 64.4$) During stimulus presentation (and thus after 2 of the 5 TMS pulses), mean eye position deviated only a very small amount, and to the left rather than right (by 0.46° of visual angle, compared to a total line length of 29° of visual angle, and an eccentricity for the left gap when present of 14°). During TMS, eye blinks occurred during stimulus presentation on less than 2% of trials. Thus, neither changes in eye position, nor blinks due to TMS, can plausibly explain the substantial impairment of detection for left gaps that we observed also in our subsequent experiments (Experiments 2 and 4). Please note also that Experiment 3 found that the same right-parietal TMS actually enhanced rather than suppressed detection of gaps when present in the right visual field instead. This opposite outcome for the other hemifield is inconsistent with any account in terms merely of TMS-induced blinks obliterating some of the visual displays.

2.3. Experiment 2: procedure

For practical reasons only 6 of the original 9 subjects were studied in this time-consuming and demanding follow-up experiment. The six subjects were aged 25–33, all male and with an Edinburgh Handedness Inventory score of 92 ± 4. The parietal hotspot was marked using the scalp coordinates for each subject from the previous experiment. However, in order to confirm that the hotspot does indeed identify the most effective site in its scalp neighbourhood, we now reassigned it as providing the centre of a new 9-point grid (4 cm × 4 cm, i.e. 2 cm between all nearest points in a square grid) which was marked on the scalp. The effect of TMS applied to all of these nine sites was then assessed, to examine how the impact on performance might vary as TMS was shifted away from the putative hotspot. Subjects again had to discriminate between left-gap and no-gap stimuli, as for Experiment 1, but now in blocks of 60 trials (30 no-gap and 30 left-gap stimuli, in randomly intermingled order, with no-gap trials now more common in order to enable formal signal-detection-theory analyses), first performed without TMS (one block, baseline), and then with TMS disruption (using exactly the same parameters as Experiment 1 and given with each trial, for 10 blocks). TMS was initially delivered over the putative parietal hotspot, and then in randomised order over the 8 other points in the new square grid centred on the hotspot. A final block was then performed with TMS again over the putative hotspot, to provide an average value for this site before and after extended experience, and to assess any impacts of practice (see Fig. 4). Thus the dual aims of Experiment 2 were to obtain confirmation of the spatial-specificity of the identified TMS hotspot, via follow-up testing of a grid of positions on the scalp centred around that site; and to do so while collecting enough psychophysical data to allow full application of signal-detection measures (including d').

2.4. Experiment 2 results: perceptual effects of parietal stimulation on sensitivity for left sided targets, with spatial-specificity of the TMS effect confirmed via the scalp-grid comparisons

Sensitivity (d') for left gaps was indeed found to be impaired during TMS over the right-parietal putative 'hotspot' (as identified by the preceding hunting procedure), and the spatial-specificity of the hotspot TMS site was then confirmed by comparing 9 TMS positions in a grid centered on the putative hotspot.

Signal-detection analysis was used to yield the sensitivity measure 'd-prime' (d') from the 6 subjects' responses, which in essence, quantifies an observer's ability to discriminate signal from noise. This was derived from the z-transformed 'Hit' (H) and 'False Alarm' (FA) rates ($d' = z(H) - z(\mathrm{FA})$) to provide a measure of sensitivity that is independent of bias or criterion. Derived in this way from two z-scores, d' is the distance between the means of the underlying noise and signal distributions, expressed in units of their common standard deviation (Green & Swets, 1966). The subjects' intrinsic bias towards giving 'yes' or 'no' responses for gap-presence was derived as the 'criterion' measure (c), where $c = -0.5\ [z(H) + z(F)]$. Criterion is independent of sensitivity in signal-detection terms, and is also expressed in standard deviation units. The effect of TMS at the right-parietal putative 'hotspot' was compared with the averaged effect of TMS applied over the 8 equally spaced surrounding sites, to determine whether or not the hunting procedure had in fact located the optimal site in its neighborhood. Although typically expressed in standard deviation units, we report d' here in terms of a proportional (%) change from the (no-TMS) baseline: [d-prime during TMS/d-prime at baseline] × 100. In this way TMS effects at different locations are all normalised relative to subjects' pre-existing level of performance. The data showed a significant difference ($t(5) = -2.59$, $p = 0.048$, two-tailed; see Fig. 3 and Table 1) between: (a) subjects' performance with TMS given over the right-parietal hotspot (where d' fell to $89 \pm 14\%$ of its baseline value), and (b) performance with TMS given over the eight surrounding sites in the grid (where d' rose to $112 \pm 9\%$ of its baseline value). Finally, there were no significant TMS impacts on criterion (c) for

Table 1
Subjects' d-prime values, expressed as a % of baseline (no-TMS) performance ([d-prime during TMS/d-prime at baseline] × 100) for each of the 9 points. The standard error of the mean is shown in parentheses.

Position relative to parietal hotspot	2 cm medial	Level	2 cm lateral
2 cm anterior	112 (12)	120 (13)	106 (11)
Level	109 (17)	89 (13)	114 (11)
2 cm posterior	119 (17)	114 (17)	103 (19)

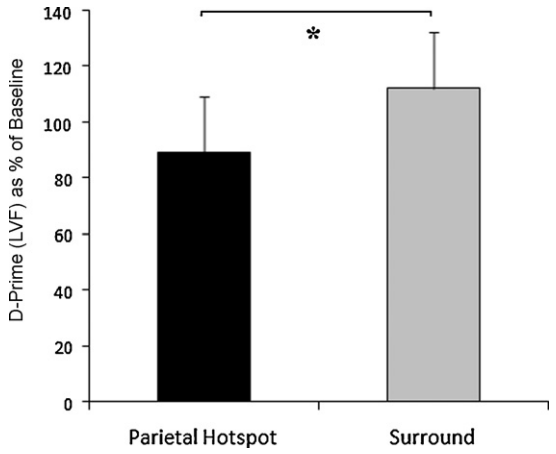

Fig. 3. Visual sensitivity (*d*-prime, as % of the no-TMS baseline: [*d*-prime during TMS/*d*-prime at baseline] × 100) in the left visual field (LVF) for Experiment 2, which found it to be significantly lower with TMS over the right-parietal hotspot as compared to the (averaged) 8 surrounding sites in the 9-point grid. The asterisk represents a significant difference between the 2 conditions; see main text. Error bars show SEM.

Table 2
Subjects' criterion values shown as the numerical deviation from baseline (no-TMS), for each of the 9 points, during TMS. The standard error of the mean is shown in parentheses.

Position relative to parietal hotspot	2 cm medial	Level	2 cm lateral
2 cm anterior	−0.05 (0.23)	0.10 (0.27)	−0.06 (0.16)
Level	−0.16 (0.16)	0.14 (0.11)	0.24 (0.21)
2 cm posterior	−0.16 (0.19)	0.10 (0.14)	0.16 (0.16)

left gaps; see Table 2 (all $p > 0.10$). The data were also plotted in block sequence order (i.e. now shown in the order of time, rather than just spatially organised); see Fig. 4. Performance over those blocks which did not involve TMS over the hotspot was examined for evidence of any ongoing learning effect. There was a modest overall increase in performance; as a linear function, d' increased by 0.030 per block (dashed line), but across all blocks d' values were not correlated significantly with block order ($r_s(6) = 0.488$, $p = 0.22$). As a precaution against potential order confounds, TMS was delivered over the right-parietal hotspot for both the first and last TMS blocks (Fig. 4), and their values averaged before comparison with the surround sites. As demonstrated in Fig. 4 the performance for both of the hotspot blocks (black symbols) was comparable despite their very different sequential position.

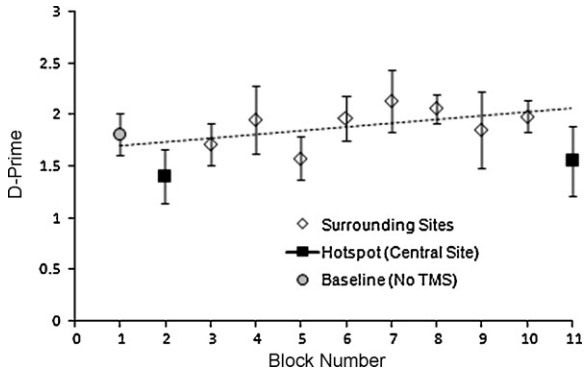

Fig. 4. *d*-Prime values from Experiment 2 are shown for the baseline condition (no-TMS, grey symbol at far left); for 10 Hz TMS over the right-parietal hotspot (black symbols, second from left and rightmost) and for 10 Hz TMS over the eight surrounding sites in the scalp grid (open symbols), plotted against sequential block order along the *x*-axis. Error bars show SEM. Performance over blocks 3–10 (those which did not involve TMS over the hotspot), was examined for evidence of any ongoing learning effect. The no-TMS value for d' at the start of the study was 1.84 ± 0.23. There was a modest overall increase in performance; as a linear function, d' increases by 0.030 per block (dashed line), but across all blocks, d' values were not correlated significantly with block order ($r_s(6) = 0.488$, $p = 0.22$). In any case, as a precaution against any increase in d' over successive blocks, TMS was delivered over the right-parietal hotspot for both the first and last TMS blocks (black symbols), and their values averaged before comparison with the surround sites. Note the comparable performance for both of the hotspot blocks (black symbols) despite their very different sequential position.

2.5. Experiment 3: procedure

In this experiment, the 6 subjects tested (including five who had participated in both Experiments 1 and 2, and one who had participated in just Experiment 1) were 5 males and 1 female, aged 25–33, with a handedness score of 92 ± 4. They were now tested in their ability to detect right sided gaps instead (Fig. 1C), when these were intermingled with no-gap stimuli (Fig. 1A) in a random order. Subjects now knew in advance that any gap could appear only on the far right. Their ability to detect such gaps was first measured without TMS (one baseline block, 60 trials as in Experiment 2, with gap presence or absence equiprobable) and then with both real or Sham TMS disruption (using the parameters stated above), during two further blocks of 60 trials. TMS was given over the same right-parietal hotspot determined by the preceding hunting procedure, with the order of real and Sham TMS blocks counterbalanced across the 6 subjects. Sham stimulation was given at the same intensity, but with the coil first rotated 90° around its (figure-of-eight) long axis before placement on the scalp. With this coil orientation no MEP is produced when held over motor cortex (even at 100% of maximum stimulator output), and substantially less intracerebral TMS-induced voltage is recorded when held over monkey parietal cortex (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001); yet comparable acoustic noise, and non-zero scalp stimulation, still occur.

Based on Hilgetag et al. (2001) and the hemispheric-competition notion of Kinsbourne (1977), as briefly reviewed in our introduction, we might expect that TMS over the right-parietal hotspot site, selected to impair detection of left gaps, might conversely enhance detection of right gaps. But if the TMS disruption for left gaps was somehow nonspecific (e.g. merely reflecting, say, induced blinks), then the same TMS should presumably impair sensitivity to right gaps in the same or similar manner to the impact on performance for left gaps, rather than having an opposite effect.

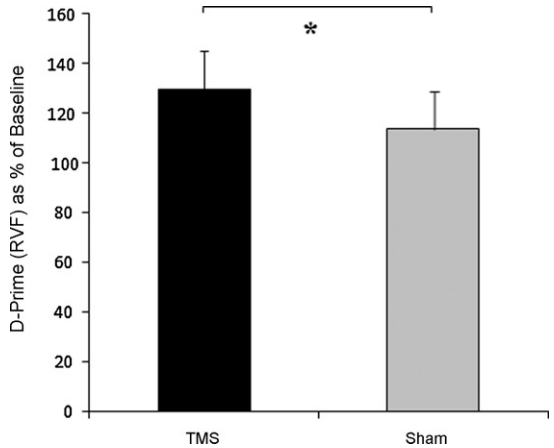

Fig. 5. The effect of TMS over the right-parietal hotspot on *d*-prime (as % of no-TMS baseline: [*d*-prime during TMS/*d*-prime at baseline] × 100) for targets in the right visual field (RVF), showing a significant rise compared to the Sham condition see main text. Error bars show SEM.

2.6. Experiment 3 results: perceptual effects of parietal stimulation on sensitivity for right sided targets

As in Experiment 2, the data were first normalised as a % of baseline (no-TMS) performance, for both real and Sham TMS conditions, i.e. [*d*-prime during TMS/*d*-prime at baseline] × 100. Compared to baseline values, sensitivity (d') for gaps in the right visual field (RVF) was found to increase during real TMS over the right-parietal hotspot (i.e. on average d' increased to 130 ± 16% of baseline values). This change was less marked during Sham TMS (d' rose only to 114 ± 15% of baseline values), leading to a significant difference between real and Sham TMS conditions ($t(5) = 4.25$, $p = 0.010$, two-tailed; see Fig. 5). Note that the enhancement by right-parietal TMS over the hotspot is the opposite outcome to the reduced sensitivity found (in Experiment 2) for gaps in the left visual hemifield. As in Experiment 2, there were no significant TMS effects on the criterion (c) measure in Experiment 3 ($p = 0.53$).

2.7. Experiment 4: procedure

The aim of this final study was to examine how TMS intensity over the right-parietal hotspot, effective in disrupting sensitivity to left gaps, might relate to individual motor thresholds when stimulating over M1 instead. 8 subjects (from the original 9 in Experiment 1, 7 male, 1 female, handedness score 82 ± 10) were asked to discriminate between 'left gap' and 'no gap' stimuli in blocks of 60 trials, just as in Experiment 2. However, blocks were now performed in successive pairs: one with TMS delivered over the right-parietal hotspot and one using Sham TMS (coil still held over the same hotspot, but now at 90° to the scalp), with the order of these TMS types within each successive block-pair counterbalanced. Each block-pair was randomly assigned 1 of 10 different TMS intensities (10% RMT, or 20% RMT, or 30% RMT, and so on up to 100% RMT) and thus each of the 10 TMS intensity levels was performed in a different, pseudorandomized order for each subject. For block-pairs, the sequence (TMS first or Sham first) alternated with each 10% increase in TMS intensity. For half the subjects (chosen at random) the sequence was: TMS first for 10% RMT, Sham first for 20% RMT, TMS first for 30% RMT and so on. For the other half, the sequence also alternated in similar fashion but starting with Sham first for 10% RMT. This was done to avoid weighting the higher TMS intensity blocks with more TMS-first block pairs (and thus to circumvent any possibility that poorer performance at higher TMS intensities might somehow reflect intra-block-pair practice effects). In this way we could determine how the impact of TMS at different intensities over the right-parietal hotspot (on visuospatial sensitivity to left gaps) might relate to the intensity of TMS required to reach resting motor threshold in individual subjects.

2.8. Experiment 4 results: relationship between perceptual effect at the parietal hotspot for different intensities, and motor threshold for each subject

For the 8 subjects tested, the RMT range was 40–69% of maximum stimulator output, with a mean of 53 ± 9.7%. For each subject, sensitivity for gaps in the left visual hemifield fell as right-parietal TMS intensity over the hotspot was increased. The rate at which this occurred was studied by comparing the change in d' after real TMS (expressed as a % of Sham TMS performance: [*d*-prime during real TMS/*d*-prime during Sham TMS] × 100), against TMS intensity (% of maximum stimulator output) in each subject, and then fitting a linear trend-line to each resulting function (the individual subject data for this is shown in Fig. 6). Further analysis tested whether the disruptive effect of right-parietal TMS (over the hotspot) at different intensities, upon visuospatial sensitivity to left gaps, was linked to subjects' RMT. If so, we would expect a given level of TMS intensity to produce more disruption in subjects with a lower RMT (and less in those with a higher RMT). We can expect accordingly that the best spread of d' values (for comparison with individual subject RMT values) should be found at a TMS intensity corresponding to the *average* RMT across subjects. For each subject, we therefore read off along their linear trend-line the % drop in d' at the average RMT (53% of maximum stimulator output). A significant correlation (Spearmans's rho, $r_s(6) = 0.794$, $p = 0.019$, two-tailed) was found between the d' drop due to TMS (at 53% of maximum stimulator output) for each subject and their RMT; see Fig. 7. Hence a key finding from Experiment 4 is that for TMS over the right-parietal hotspot, the amount by which left-gap-sensitivity declines (relative to sham) at a given level of TMS intensity relates systematically to each individuals' resting motor threshold. Since the latter can be readily assessed for any healthy subject or patient, it can now provide a natural way to scale TMS intensity when targeting a right-parietal site with the aim of changing visuospatial sensitivity for peripheral targets, as for the gaps used here. Note that this may not always apply for other TMS effects, for which scaling by motor threshold may be inappropriate (see Stokes et al., 2005, 2007, plus Antal, Nitsche, Kincses, Lampe, & Paulus, 2004; Boroojerdi et al., 2002; Stewart, Walsh, & Rothwell, 2001). Here we have been able to show that the approach is viable for right-parietal TMS effects upon visuospatial sensitivity for left gaps.

We next examined the 8 structural MRI scans of the subjects participating in Experiment 4, to investigate possible underlying causes of the correlation described above (as illustrated in Fig. 7). We found that the reconstructed scalp-to-cortex depths at each individual parietal or motor hotspot (for parietal, the mean depth was 16.2 mm, SD 2.5 mm; for motor this was 14.0 mm, SD 2.5 mm) correlated tightly with the other depth in a subject-by-subject manner ($r_s(6) = 0.94$, $p < 0.05$, two-tailed). To assess the influence of scalp-cortex distance on the relationship we had found between individuals' RMT and their susceptibility to parietal-hotspot TMS (Fig. 7), we next performed partial correlations, now entering the individual scalp-cortex depths at parietal or motor hotspots as further controlling factors. Either of these each rendered the original correlation less significant. Specifically, entering RMT as factor *W*, % real versus Sham d' at mean RMT as factor *X*, scalp-to-cortex distance for the parietal hotspot as factor *Y*, and this distance for the motor hotspot as factor *Z*, yielded: $r_s(5)_{WXY} = 0.72$, $t = 2.10$, $p = 0.10$, and $r_s(5)_{WXZ} = 0.70$, $t = 1.92$, $p = 0.13$. This implies that individual differences in scalp-to-cortex depth contribute to the observed relationship between individual RMTs and the impact of parietal-hotspot TMS on left-gap sensitivity (Fig. 7). This does not, however, undermine the usefulness of scaling TMS intensity relative to RMT, when seeking an individually effective TMS intensity for the parietal hotspot.

3. General discussion

This study introduces, explores and validates a novel hunting procedure for identifying a distinct point over right posterior parietal cortex at which TMS disrupts visuospatial sensitivity in the contralateral visual hemifield; while leading to enhanced visuospatial sensitivity instead for the ipsilateral hemifield. The right-parietal site identified lies along the antero-superior edge of parietal regions commonly implicated in 'neglect-related' lesions (such as the temporo-parietal junction, angular and supramarginal gyri, see Golay, Schnider, & Ptak, 2008; Parton & Husain, 2004), though it should be noted that extensive lesions after stroke versus TMS disruption in normals, as here, may be very different in their physiological consequences. The location of the identified effective TMS site along the anterior intraparietal sulcus (IPS) appears consistent with several other TMS studies in normals that disrupted visuospatial processing (e.g. Fierro et al., 2000; Hilgetag

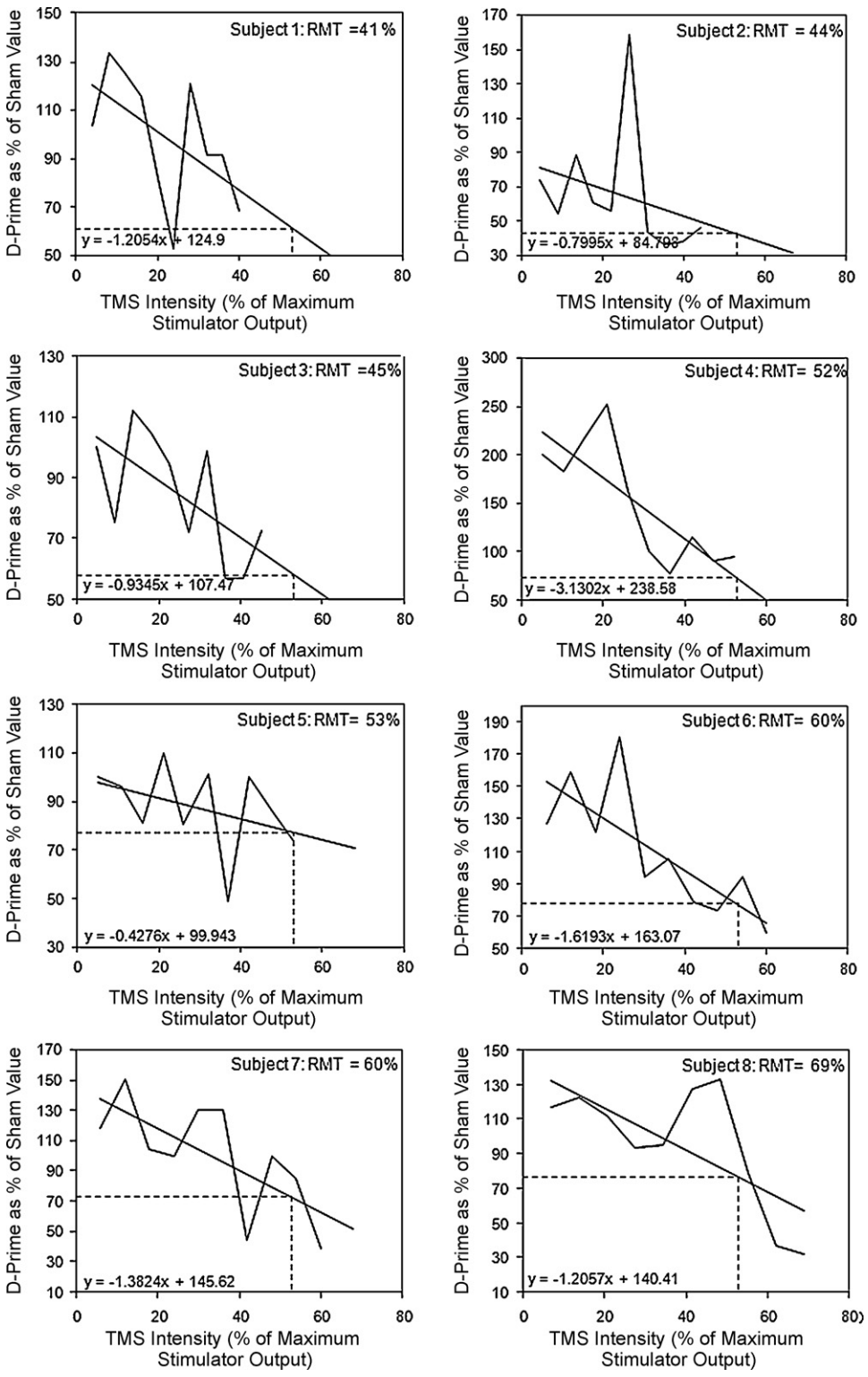

Fig. 6. The individual subject plots for data from Experiment 4, displayed in order of increasing RMT (as shown in the top right corner of each plot) showing the fall in d' for left gaps with increased intensity of TMS over the right-parietal hotspot. *d*-Prime is shown (along the *y*-axis) as a % of the corresponding Sham value and TMS intensity as % of maximum stimulator output along the *x*-axis. A linear trend-line is fitted to each plot, with the function equation displayed in the bottom left hand corner of each plot. The d' value (as a % of Sham) at a constant reference TMS intensity (i.e. at a stimulator output of 53% corresponding to the grand mean of all subjects' RMT – see main text) is calculated for each subject (represented by the dashed lines). These values were then used in the correlation with individual subject RMTs (cf. Fig. 7).

et al., 2001; Oliveri, Rossini, Pasqualetti, et al., 1999; Sack et al., 2007; Schenkluhn, Ruff, Heinen, & Chambers, 2008). Here we introduce a systematic and cross-validated way to identify the optimal site functionally, and at an effective TMS intensity, for individual subjects.

The cross-validation of the hotspot's properties included: (a) our confirmation of genuine effects upon visuospatial sensitivity (d'), with signal-detection measures (Experiments 2–4); (b) confirmation that the site yielded by our hunting procedure was indeed significantly the most effective within a 9-point grid

subsequently tested around it, via collection of further data independent of the original hunting procedure (Experiment 2); (c) demonstration that sensitivity to targets in the right visual hemifield actually showed the opposite pattern to left hemifield targets, for the same right-parietal TMS site, with enhanced sensitivity for right targets (Experiment 3) but impaired for left targets (Experiments 2 and 4); and finally (d) demonstration in Experiment 4 that the effect of right-parietal TMS as a function of intensity related systematically to each individual's motor threshold for TMS over M1 (in a manner that may in turn relate to scalp-to-cortex depths, as implied by partial correlations with those for both parietal and M1 sites).

The opposite pattern of effects for left versus right hemifield visuospatial sensitivity (i.e., impaired sensitivity for the left hemifield, but enhanced sensitivity for the right during our right-parietal TMS) rules out a nonspecific disruption of all visual processing (as might have arisen if, say, our TMS had induced actual blinks, or some internal 'attentional blink' regardless of target location). The opposing pattern for the two hemifields accord with classic notions of hemispheric rivalry (Kinsbourne, 1977) and with other TMS work (Hilgetag et al., 2001), though now confirming this opposing pattern for actual perceptual sensitivity, d', in signal-detection terms for the first time.

Future studies using variations on the new paradigm introduced here could study the timing of these TMS effects in more detail, either by using single TMS pulses at different points in time relative to the visual displays, and/or by jittering the 10 Hz bursts relative to those stimuli. One further refinement to the paradigm for future work would be to incorporate trials without TMS as a within-session baseline and thus fully integrate the no-TMS condition in terms of block performance-order. The 9 subjects we tested were naïve to the change in gap-present proportions (from 50% to 90%) when moving from the initial 'staircase' thresholding stage to the hunting procedure of Experiment 1. This may be an important consideration for future studies utilising a similar procedure, as if subjects were cognizant of the change, a problematic liberal shift in their response criteria might occur.

It has been suggested that when judging non-foveal targets (such as an eccentric 'gap' in the extended horizontal line here) several processes occur that draw on specific circuits involving the parietal cortex. Such processes include decoupling attention from fixation and shifting the attentional focus covertly to a target location (Giesbrecht & Mangun, 2005; Posner, Walker, Friedrich, & Rafal, 1984). In the present experiments, the possible location of the gap target on one or other side was always known in advance, and the burst of TMS pulses began shortly before display onset. Therefore the first pulse in this burst may have contributed to the overall effect on visual sensitivity by disrupting the intended covert attentional focus. A recent brain imaging study compared activation during holding or shifting of covert attention for both central and peripheral locations (Kelley, Serences, Giesbrecht, & Yantis, 2008). Their analysis revealed activity during maintenance of covert attention at *peripheral* locations (during central eye fixation, as here) in anterior PPC, with a peak approximately 1 cm medial to the location found in the present study. This activation for maintained peripheral attention fell closer to our stimulation site than those for shifting attention from central fixation to periphery. This may accord with our present use of a paradigm in which the peripheral target location was foreknown and constant, and which required covert attention to be held at the target location rather than frequently shifted.

The 'hunting procedure' introduced in Experiment 1 is intended to provide a quick and practical heuristic for locating a right-parietal area that influences visuospatial sensitivity. Despite this brevity, the risk of falsely identifying the wrong area as the 'hot spot' appears relatively low. If we suppose that subjects responded entirely at random, the probability of scoring 4 initial consecutive hits followed by 4 consecutive misses (as the 'hotspot' was defined) would be 0.0039 for a given test location (i.e. $p(\text{correct})^4 \times p(\text{incorrect})^4 = 0.5^4 \times 0.5^4 = 3.9 \times 10^{-3}$). However if subjects maintain the 95% correct performance level achieved during the 'staircase' thresholding trials, the risk of a false positive during the hunting procedure arguably is lower still, at just 5.1×10^{-6} per stimulation site ($p(\text{correct})^4 \times p(\text{incorrect})^4 = 0.95^4 \times 0.05^4 = 5.1 \times 10^{-6}$). Data from Experiment 4 reveal how well subjects actually maintained their % correct performance under conditions that mimic the hunting procedure (recall that in this experiment, one of the blocks was performed with Sham TMS given over the hotspot at 100% RMT). The average % correct score from this block for all subjects was $85 \pm 7\%$ (understandably less than the 95% scored without any distraction from the coil, but far greater than chance levels of accuracy). When we insert this value into our previous hypothetical calculation, the probability of finding a false hotspot remains very low: $0.85^4 \times 0.15^4 = 2.6 \times 10^{-4}$ per TMS site tested. Thus we suggest that despite its simplicity and speed, the hunting procedure introduced in Experiment 1 should not be particularly susceptible to false-positive 'hotspots'.

As touched on in Section 2.1, a slight spatial 'sampling-bias' might still arise during the hunting procedure, despite the alternating start direction of the spiral path. Because the spiral search pattern ran clockwise for all subjects during the hunting procedure, anterior–lateral and posterior–medial points would be sampled somewhat later. However by analysing the actual sampling paths of all subjects we found that the anterior–lateral or posterior–medial locations (when grouped into quadrants) were tested only 0.8 (on average) sites later than the other two quadrants. As implemented, our hunting procedure thus seems sufficiently robust in practice not to be substantially affected by spatial sampling-bias, though for future work any such bias could be reduced still further by adding anterior and posterior starting directions (to the existing medial and lateral ones).

The significant correlation between the effectiveness of parietal TMS (on visuospatial sensitivity) at different intensities, with motor threshold in individual subjects here, builds on a previous observation (Oliveri, Caltagirone, et al., 2000) that the average level of TMS intensity (given over P4 in that study) required to disrupt tactile perception can relate to RMT. It contrasts however with other work reporting little or no correlation of RMT with phosphene thresholds over occipital cortex (Antal et al., 2004; Boroojerdi et

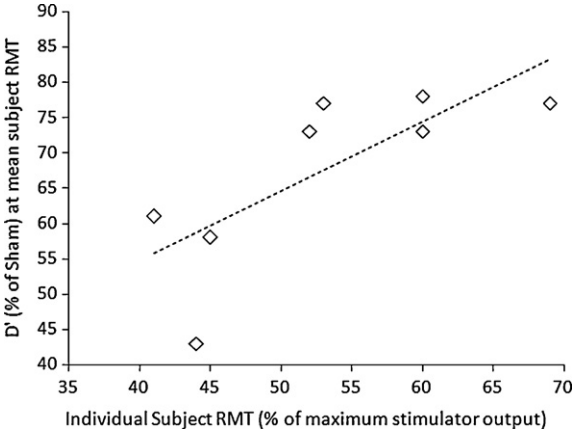

Fig. 7. Scatterplot illustrating the positive correlation (dotted line: $r_s(6) = 0.79$, $p = 0.019$) between the d' drop (expressed as a % of d' scores during Sham rather than real TMS) along the *y*-axis for each subject (at the average RMT *across* subjects, i.e. 53% of maximum stimulator output), with each subject's individual RMT shown along the *x*-axis, for the 8 subjects of Experiment 4.

al., 2002; Stewart et al., 2001). The latter outcome might reflect idiosyncrasies in the depth of early visual cortical structures (from the scalp) in individuals (cf. Stokes et al., 2005). By contrast in our subjects, the MR-reconstructed depth from the scalp, to parietal or motor cortex under either of our hotspot sites, did show parietal–motor correlations. Subsequent partial correlations implicated this underlying scalp-to-cortex anatomical relationship as one contributor to the initial correlation demonstrated in Experiment 4 (and Fig. 7), between individual RMT, and the impact of real versus Sham parietal-hotspot TMS on left-visuospatial sensitivity. Nevertheless, our data still show that by using TMS (over the individually hunted, functional defined parietal hotspot) at an intensity equal to the individually determined RMT over M1, one can expect to obtain a reliable effect on visuospatial sensitivity.

Given the greater scalp-to-cortex distance for the parietal than the motor site, over-stimulation of underlying parietal cortex seems unlikely. Thus right-parietal TMS at the spot identified via our "hunting" procedure, at an intensity equal to RMT, should have the dual virtues of inducing a robust effect on visuospatial sensitivity (as shown in Experiments 2 and 4, see Figs. 3 and 7) yet with a low risk of any adverse effect. Experiment 4 also illustrates the potential importance of tailoring the intensity of stimulation used in each subject (e.g. in relation to RMT) rather than using a single constant intensity across subjects (which may result in over-or under stimulation of the underlying cortex for some subjects). Contrary to studies on earlier visual areas (Antal et al., 2004; Boroojerdi et al., 2002; Stewart et al., 2001) – which may be distinct for the reasons noted earlier, such as highly variable distance from the scalp – RMT may thus still provide a useful and easily measured physiological surrogate for other TMS sites, in this case for the intensity of stimulation over right-parietal cortex needed to disrupt visuospatial sensitivity.

4. Conclusion

In this study we identified a right-parietal 'hotspot' or node that may form a pivotal part of the network that subserves visuospatial awareness. The use of signal-detection theory revealed significant impacts on true visual sensitivity (i.e. d'), with right-parietal TMS at the identified hotspot site, with an appropriate intensity, disrupting visuospatial sensitivity for left targets but enhancing this for right targets. We cross-validated the derived parietal site in several ways, to confirm the efficacy of our new hunting procedure. This provides a systematic new way to identify an effective right-parietal site for inducing specific effects on visuospatial sensitivity, with the effective intensity now also being guided in a principled manner by that 'anchor' for TMS researchers, the RMT.

References

Antal, A., Nitsche, M., Kincses, T., Lampe, C., & Paulus, W. (2004). No correlation between moving phosphene and motor thresholds: A transcranial magnetic stimulation study. *Neuroreport*, *15*(2), 297–302.

Ashbridge, E., Walsh, V., & Cowey, A. (1997). Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia*, *35*(8), 1121–1131.

Beckers, G., & Hömberg, V. (1992). Cerebral visual motion blindness: Transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proceedings of the Royal Society of London, Biological Sciences*, *249*, 173–178.

Bjoertomt, O., Cowey, A., & Walsh, V. (2002). Spatial neglect in near and far space investigated by repetitive transcranial magnetic stimulation. *Brain*, *125*(9), 2012–2022.

Blankenburg, F., Ruff, C. C., Bestmann, S., Bjoertomt, O., Eshel, N., Josephs, O., et al. (2008). Interhemispheric effect of parietal TMS on somatosensory response confirmed directly with concurrent TMS–fMRI. *The Journal of Neuroscience*, *28*(49), 13202–13208.

Boroojerdi, B., Meister, I., Foltys, H., Sparing, R., Cohen, L., & Töpper, R. (2002). Visual and motor cortex excitability: A transcranial magnetic stimulation study. *Clinical Neurophysiology*, *113*(9), 1501–1504.

Brasil-Neto, J. P., McShane, L. M., Fuhr, P., Hallett, M., & Cohen, L. G. (1992). Topographic mapping of the human motor cortex with magnetic stimulation: Factors affecting accuracy and reproducibility. *Electroencephalography and Clinical Neurophysiology*, *85*(1), 9–16.

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., La Bua, V., Daniele, O., et al. (2003). 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neuroscience Letters*, *336*(2), 131–133.

Chambers, C. D., Stokes, M. G., Janko, N. E., & Mattingley, J. B. (2006). Enhancement of visual selection during transient disruption of parietal cortex. *Brain Research*, *1097*(1), 149–155.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215.

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Töpper, R., et al. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, *1072*(1), 194–199.

Ellison, A., Schindler, I., Pattison, L., & Milner, D. (2004). An exploration of the role of the superior temporal gyrus in visual search and spatial perception using TMS. *Brain*, *127*(10), 2307–2315.

Fecteau, S., Pascual-Leone, A., & Théoret, H. (2006). Paradoxical facilitation of attention in healthy humans. *Behavioural Neurology*, *17*(3–4), 159–162.

Fierro, B., Brighina, F., Giglia, G., Palermo, A., Francolini, M., & Scalia, S. (2006). Paired pulse TMS over the right posterior parietal cortex modulates visuospatial perception. *Journal of the Neurological Sciences*, *247*(2), 144–148.

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., et al. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport*, *11*(7), 1519–1521.

Giesbrecht, B., & Mangun, G. R. (2005). Identifying the neural systems of top down attentional control: A meta-analytic approach. In L. Itti, G. Rees, & J. Tsotsos (Eds.), *Neurobiology of attention* (pp. 53–56). New York: Academic Press/Elsevier.

Golay, L., Schnider, A., & Ptak, R. (2008). Cortical and subcortical anatomy of chronic spatial neglect following vascular damage. *Behavioural and Brain Functions*, *4*, 43.

Green, D. M., & Swets, J. A. (1966). *Signal detection and psychophysics*. New York: John Wiley and Sons.

Hilgetag, C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nature Neuroscience*, *4*(9), 953–957.

Jin, Y., & Hilgetag, C. (2008). Perturbation of visuospatial attention by high-frequency offline rTMS. *Experimental Brain Research*, *189*(1), 121–128.

Kelley, T. A., Serences, J. T., Giesbrecht, B., & Yantis, S. (2008). Cortical mechanisms for shifting and holding visuospatial attention. *Cerebral Cortex*, *18*(1), 114–125.

Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. In E. A. Weinstein, & R. P. Friedland (Eds.), *Hemi-inattention and hemisphere specialisation. Advances in neurology* (pp. 41–49). New York: Raven Press.

Koch, G., Oliveri, M., Cheeran, B., Ruge, D., Lo Gerfo, E., Salerno, S., et al. (2008). Hyperexcitability of parietal–motor functional connections for the intact left-hemisphere in neglect patients. *Brain*, *131*(12), 3147–3155.

Koch, G., Oliveri, M., Torriero, S., & Caltagirone, C. (2005). Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. *Experimental Brain Research*, *160*(4), 510–516.

Lisanby, S., Gutman, D., Luber, B., Schroeder, C., & Sackeim, H. (2001). Sham TMS: Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry*, *49*(5), 460–463.

Meister, I. G., Wienemann, M., Buelte, D., Grünewald, C., Sparing, R., Dambeck, N., et al. (2006). Hemiextinction induced by transcranial magnetic stimulation over the right temporo-parietal junction. *Neuroscience*, *142*(1), 119–123.

Mort, D., Malhotra, P., Mannan, S., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain*, *126*(9), 1986–1997.

Muggleton, N., Cowey, A., & Walsh, V. (2008). The role of the angular gyrus in visual conjunction search investigated using signal detection analysis and transcranial magnetic stimulation. *Neuropsychologia*, *46*(8), 2198–2202.

Muggleton, N., Postma, P., Moutsopoulou, K., Nimmo-Smith, I., Marcel, A., & Walsh, V. (2006). TMS over right posterior parietal cortex induces neglect in a scene-based frame of reference. *Neuropsychologia*, *44*(7), 1222–1229.

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., et al. (2004). Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. *Neuroimage*, *21*(1), 99–111.

Oliveri, M., Caltagirone, C., Filippi, M., Traversa, R., Cicinelli, P., Pasqualetti, P., et al. (2000). Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. *The Journal of Physiology*, *529*(2), 461–468.

Oliveri, M., Rossini, P., Filippi, M., Traversa, R., Cicinelli, P., Palmieri, M., et al. (2000). Time-dependent activation of parieto-frontal networks for directing attention to tactile space. *Brain*, *123*(9), 1939–1947.

Oliveri, M., Rossini, P. M., Pasqualetti, P., Traversa, R., Cicinelli, P., Palmieri, M., et al. (1999). Interhemispheric asymmetries in the perception of unimanual and bimanual cutaneous stimuli. A study using transcranial magnetic stimulation. *Brain*, *122*(9), 1721–1729.

Oliveri, M., Rossini, P. M., Traversa, R., Cicinelli, P., Filippi, M. M., Pasqualetti, P., et al. (1999). Left frontal transcranial magnetic stimulation reduces contralateral extinction in patients with unilateral right brain damage. *Brain*, *122*(9), 1731–1739.

O'Shea, J. O., & Walsh, V. (2007). Transcranial magnetic stimulation. *Current Biology*, *17*(6), R196–R199.

Parton, A., & Husain, M. (2004). Spatial neglect. *Advances in Clinical Neuroscience and Rehabilitation*, *4*(4), 17–18.
Pascual-Leone, A., Bartres-Faz, D., & Keenan, J. P. (1999). Transcranial magnetic stimulation: Studying the brain–behaviour relationship by induction of 'virtual lesions'. *Philosophical Transactions of the Royal Society of London B*, *354*, 1229–1238.
Pascual-Leone, A., Gomez-Tortosa, E., Grafman, J., Alway, D., Nichelli, P., & Hallett, M. (1994). Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology*, *44*(3), 494–498.
Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience*, *4*(7), 1863–1874.
Pourtois, G., Vandermeeren, Y., Olivier, E., & de Gelder, B. (2001). Event related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference. *Neuroreport*, *12*(11), 2369–2374.
Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, *91*(2), 79–92.
Ryan, S., Bonilha, L., & Jackson, S. (2006). Individual variation in the location of the parietal eye fields: A TMS study. *Experimental Brain Research*, *173*(3), 389–394.
Sack, A., Cohen Kadosh, R., Schuhmann, T., Moerel, M., Walsh, V., & Goebel, R. (2009). Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods. *The Journal of Cognitive Neuroscience*, *21*(2), 207–221.
Sack, A., Kohler, A., Bestmann, S., Linden, D., Dechent, P., Goebel, R., et al. (2007). Imaging the brain activity changes underlying impaired visuospatial judgements: Simultaneous FMRI TMS, and behavioral studies. *Cerebral Cortex*, *17*(12), 2841–2852.
Schenkluhn, B., Ruff, C., Heinen, K., & Chambers, C. (2008). Parietal stimulation decouples spatial and feature-based attention. *The Journal of Neuroscience*, *28*(44), 11106–11110.
Seyal, M., Ro, T., & Rafal, R. (1995). Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe. *Annals of Neurology*, *38*(2), 264–267.
Stewart, L., Walsh, V., & Rothwell, J. (2001). Motor and phosphene thresholds: A transcranial magnetic stimulation correlation study. *Neuropsychologia*, *39*(4), 415–419.
Stokes, M. G., Chambers, C. D., Gould, I. C., English, T., McNaught, E., McDonald, O., et al. (2007). Distance adjusted motor threshold for transcranial magnetic stimulation. *Clinical Neurophysiology*, *118*(7), 1617–1625.
Stokes, M. G., Chambers, C. D., Gould, I. C., Henderson, T. R., Janko, N. E., Allen, N. B., et al. (2005). Simple metric for scaling motor threshold based on scalp-cortex distance: Application to studies using transcranial magnetic stimulation. *The Journal of Neurophysiology*, *94*(6), 4520–4527.
Sykora, S. (2005). K-space formulation of MRI. In S. Sykora (Ed.), *Stan's library* http://www.ebyte.it/library
Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. Stuttgart: Thieme.
Valero-Cabré, A., Rushmore, R., & Payne, B. (2006). Low frequency transcranial magnetic stimulation on the posterior parietal cortex induces visuotopically specific neglect-like syndrome. *Experimental Brain Research*, *172*(1), 14–21.
Walsh, V. (1998). Brain mapping: Faradization of the mind. *Current Biology*, *8*(1), R8–R11.
Wieczorowski, M. (2001). Spiral sampling as a fast way of data acquisition in surface topography. *International Journal of Machine Tools & Manufacture*, *41*, 2017–2022.