doi:10.1093/brain/awn273 *Brain* (2008), **131**, 3147–3155

Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect

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Hemispatial neglect is common after unilateral brain damage, particularly to perisylvian structures in the right-hemisphere (RH). In this disabling syndrome, behaviour and awareness are biased away from the contralesional side of space towards the ipsilesional side. Theoretical accounts of this in terms of hemispheric rivalry have speculated that the intact left-hemisphere (LH) may become hyper-excitable after a RH lesion, due to release of inhibition from the damaged hemisphere. We tested this directly using a novel twin-coil transcranial magnetic stimulation (TMS) approach to measure excitability within the intact LH of neglect patients. This involved applying a conditioning TMS pulse over left posterior parietal cortex (PPC), in order to test its effect on the amplitude of motor evoked potentials (MEPs) produced by a subsequent test pulse over left motor cortex (M1). Twelve RH stroke patients with neglect, an age-matched group of eight RH stroke patients without neglect, and 10 healthy controls were examined. We found that excitability of left PPC-M1 circuits was higher in neglect patients than the other groups, and related to the degree of neglect on clinical cancellation tests. A follow-up found that 1 Hz repetitive TMS over left PPC normalized this over-excitability, and also ameliorated visual neglect on an experimental measure with chimeric objects. Our results provide 'direct' evidence for pathological over-excitability of the LH in the neglect syndrome, as quantified by left PPC influences on left M1, with implications for possible treatment.

Keywords: neglect syndrome; transcranial magnetic stimulation; connectivity; rTMS; parietal cortex; cortical excitability

Abbreviations: ISI = inter-stimulus interval; LH = left hemisphere; MEPs = motor evoked potentials; PPC = posterior parietal cortex; RH = right hemisphere; rTMS = repetitive TMS; TMS = transcranial magnetic stimulation

Received May 10, 2008. Revised September 9, 2008. Accepted September 22, 2008. Advance Access publication October 22, 2008

Introduction

Hemispatial neglect is a common and disabling syndrome following unilateral brain damage, particularly to the right hemisphere (RH; see Heilman *et al.*, 2000; Karnath *et al.*, 2002; Driver *et al.*, 2004, for reviews). In many cases neglect is associated with haemorrhagic or ischemic stroke to right perisylvian regions, often including the right inferior parietal lobe and/or nearby temporo-parietal junction (Bisiach *et al.*, 1986; Bowen *et al.*, 1999; Karnath *et al.*, 2002; Mort *et al.*, 2003). Neglect is a multi-component syndrome that includes failures to acknowledge or explore stimuli towards the contralesional side of space (Bisiach *et al.*, 1986; Beschin and Robertson, 1997; Heilman *et al.*, 1985; Bisiach, 1991; Vallar *et al.*, 2003; Driver *et al.*, 2004). Intentional neglect or directional hypokinesia may be an additional aspect in some cases who can show difficulties in

moving towards the contralesional hemispace (Mattingley *et al.*, 1998). Patients may show intentional neglect even if they have little or no contralesional weakness (Laplane and Degos, 1983).

One influential proposal about the mechanisms contributing to neglect has invoked 'hemispheric rivalry' or competition (Kinsbourne, 1977, 1993, 1994). Normal individuals may have a dynamic balance between circuits in the two hemispheres, with appropriate activation of left-hemisphere (LH) structures tending to shift attention and spatial behaviour rightwards, but analogous activation of RH structures tending to oppose or counterbalance this. From this perspective, the RH lesions that typically induce left neglect may lead to pathological over-excitability of LH circuits, due to release from rivalry. While there have been many studies of neglect that invoked this view or extended it (Kinsbourne, 1977, 1993, 1994; Oliveri *et al.*, 1999), there have been surprisingly few studies if any that 'directly' tested for hyper-excitability within the intact LH itself. Here we sought to address this by applying twin-coil, transcranial magnetic stimulation (TMS) methods to the intact LH of patients suffering from neglect after RH strokes.

Recent anatomical and functional neuroimaging studies have potentially implicated altered patterns of cortico-cortical connectivity or coupling in neglect. For instance, neglect symptoms can arise after damage to the superior and longitudinal fasciculi (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten *et al.*, 2005; Bartolomeo *et al.*, 2007). More generally, recent neglect research has begun to emphasize that changes in inter-regional influences, between remote parts of an interconnected network, may contribute to neglect and be pathologically altered by the typical RH lesion (Corbetta *et al.*, 2005; Thiebaut de Schotten *et al.*, 2005; Bartolomeo, 2006; He *et al.*, 2007). This might lead to changes in the interactions or balance of intact left parietal cortex relative to other areas.

In separate studies of neurologically healthy subjects, we recently introduced (Koch *et al.*, 2007, 2008) a new method for non-invasive study in humans of functional influences from the posterior parietal cortex (PPC), upon ipsilateral motor cortex, M1, via a twin-coil or 'paired-pulse' TMS paradigm. A conditioning TMS pulse is applied over PPC, shortly prior to a test pulse over the hand area of ipsilateral M1. The latter pulse evokes a small twitch in contralateral hand muscles that can be measured with surface Electromyographic (EMG). In normals, when the interval between the PPC pulse and the M1 pulse is brief (~4–6 ms), the EMG response triggered by the M1 pulse is enhanced (Koch *et al.*, 2007), indicating that the PPC stimulation has a remote influence on M1. The timing and intensity of the paired pulses required to induce this effect suggest that it involves cortico–cortico pathways between the two sites of stimulation. The site of the conditioning PPC pulse that led to the most pronounced impact on M1 (Koch *et al.*, 2007, 2008) lay over the caudal part of the intraparietal sulcus, presumably activating a pathway that may involve the superior longitudinal fasciculus.

The present study applied this paired-pulse TMS method over the LH of 12 patients with neglect after RH stroke, in order to provide a 'direct' test of the idea that the LH may become hyper-excitable, now as measured for the influence of left PPC on left M1. The results were compared with a group of age-matched RH stroke patients without neglect, plus a group of healthy controls.

In a follow-up study, we also applied repetitive TMS (rTMS) over left PPC in a subset of neglect patients, an intervention that has been reported to transiently ameliorate neglect (Brighina *et al.*, 2003). We examined whether this intervention reduced neglect for our patients on an experimental measure (involving chimeric visual objects) used in other recent rehabilitative studies (Sarri *et al.*, 2006). We also assessed whether the rTMS intervention would normalize the hyper-excitable left PPC-M1 influences that we had uncovered in our first experiment.

Materials and Methods

Subjects

Twenty consecutive patients with RH damage, as confirmed by radiological (CT or MRI) and clinical examination, entered the study. All had suffered an ischemic stroke. None had any history or evidence of dementia or psychiatric disorder. All were examined in the sub-acute phase on a rehabilitation ward, within 1–6 months from onset of symptoms. All were given a standard clinical neurological and neuropsychological examination to assess any sensory or motor deficits, language disturbances or cognitive impairment, and critically the presence or absence of left neglect as assessed with conventional pen-and-paper tests. These simple tests are sufficient to diagnose the possible presence of neglect, although they do not distinguish in detail between different possible sub-types of neglect. Diagnosis of visuospatial neglect was based on the following clinical tests: copying a scene (comprising two trees, a house and a fence); line cancellation; and letter cancellation. Line cancellation was tested by presenting 30 bars, each of 4 cm, distributed with random orientations across a 257 × 364 mm sheet of paper. The centre of the sheet was aligned with the patient's sagittal body plane. Total number of cancelled bars and of omissions were calculated, for each half (left or right) of the sheet. The letter cancellation task comprised an array of 90 randomly distributed target letters (Hs) intermingled with 180 distractor items. The centre of the stimulus array was again aligned with the patient's sagittal body plane, and patients were instructed to mark all the target letters they could detect during a time period of 3 min. Total number of cancelled letters and omissions were calculated for each side of the sheet.

As a result of this assessment, 12 patients were included in the neglect group, while eight patients who did not show any symptoms related to the neglect spectrum were assigned to the no-neglect group (Table 1). These two groups of patients did not differ in mean age, gender or duration of illness.

To provide an overview of the extent of brain lesions in the patients, CT or MRI images were reconstructed for each patient and the areas of damage plotted using MRIcro software (www.sph.sc.edu/comd/rorden/mricro.html), with a graphics

Table 1 Clinical characteristics of neglect and non-neglect stroke patients participating in the study

	Gender	Age (years)	Time since stroke (days)	Line cancellation [total responses (L/R omissions)]	Letter cancellation [total responses (L/R omissions)]
Neglect patients					
1	M	64	172	15 (13/2)	55 (35/10)
2	M	79	121	5 (15/10)	49 (41/0)
3	M	38	58	25 (5/0)	68 (22/0)
4	F	71	32	24 (6/0)	51 (28/11)
5	F	74	36	28 (2/0)	42 (37/11)
6	F	57	108	26 (4/0)	50 (32/8)
7	M	54	41	29 (1/0)	11 (40/29)
8	M	49	37	13 (15/2)	29 (45/16)
9	M	65	125	26 (4/0)	72 (12/6)
10	F	76	68	19 (11/0)	59 (28/13)
11	M	60	159	22 (8/0)	64 (19/7)
12	F	71	142	18 (12/0)	41 (39/10)
Mean		63.2	91.6	20.8	49.3
SD		12.2	51.9	7.1	17.1
Non-neglect patients					
1	M	72	118	30 (0/0)	90 (0/0)
2	F	79	158	29 (1/0)	90 (0/0)
3	F	53	142	30 (0/0)	84 (6/0)
4	F	67	91	30 (0/0)	90 (0/0)
5	M	49	31	30 (0/0)	90 (0/0)
6	M	66	52	30 (0/0)	90 (0/0)
7	M	48	36	29 (1/0)	90 (0/0)
8	F	64	87	30 (0/0)	88 (2/0)
Mean		63.4	83.9	29.6	89.2
SD		10.2	45.5	0.7	1.9

tablet (WACOM Intuos A6), by a neurologist who was blind to the TMS results and the clinical scores when plotting the lesions. A T_1-weighted template comprising 12 axial slices was used to demarcate lesions for every patient.

A further healthy group of ten age-matched, neurologically-normal volunteers (five men and five women, 45- to 72-year-old) participated for completeness.

All subjects were right-handed, according to the Edinburgh inventory (Oldfield, 1971). They all gave informed consent for participation in the study, and experimental procedures were approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Experimental procedures

Experiment 1: Twin-coil TMS test of PPC-MI influences in the intact LH

EMG recordings were made from the first dorsal interosseous muscles using 9 mm diameter, Ag–AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the right index finger. Responses were amplified with a Digitimer D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK), through filters set at 20 Hz and 2 kHz with a sampling rate of 5 kHz, then recorded by a computer using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK). We used a paired-pulse TMS technique with two high-power Magstim 200 machines (Magstim Co., Whitland, Dyfed, UK). The magnetic stimulus had a nearly monophasic pulse configuration with a rise time of ~100 μs, decaying back to zero over ~0.8 ms.

As described in our recent study of normals (Koch *et al.*, 2007, 2008), the intensity of the test M1 TMS pulse (applied over left M1 here) was adjusted to evoke an MEP of ~1 mV peak-to-peak in the relaxed right dorsal interosseous muscle. The scalp location for the hand motor area of left M1 was defined as the point where stimulation evoked the largest MEP from this contralateral muscle. The test stimulator was connected to a small custom figure-of-eight-shaped coil (external diameter 50 mm). In order to stimulate M1, the coil was always placed tangentially to the scalp at a 45° angle to the midline, in order to induce a posterior-anterior current flow across the central sulcus.

The conditioning stimulator for left PPC was connected to a larger figure-of-eight-shaped coil, 70 mm in external diameter. The coil position for left PPC TMS was then defined relative to the P3 position of the 10–20 EEG system (see also Koch *et al.*, 2007, 2008). According to previous investigations, 3D MRI reconstruction for this scalp site falls over the inferior parietal lobule, close to the posterior part of the adjoining intraparietal sulcus (Herwig *et al.*, 2003; Rushworth and Taylor, 2006; Koch *et al.*, 2007). The centre of the conditioning left PPC coil was positioned tangentially to the skull, with the handle pointing downward and slightly medial (10°) in order to induce a posterior–anterior directed current in the underlying cortical tissue.

We defined the resting motor threshold as the lowest intensity that evoked five small motor evoked potentials (~50 μV) on EMG, for a series of 10 stimuli applied over M1 when the subject kept muscles relaxed in both hands, in accord with the standard international procedure (Rossini *et al.*, 1994). The intensity of the conditioning left PPC stimulus was adjusted to be either suprathreshold (110% of

resting motor threshold) or subthreshold (90%) with respect to the resting measure. The latter was evaluated using the larger figure of eight coil over left M1, with posterior–anterior orientation.

Inter-stimulus intervals between the conditioning PPC pulse and test M1 pulse were 2, 4, 6, 8, 10 or 15 ms, selected equiprobably and randomly. In two separate blocks the conditioning intensity was set either at 110% or 90% of resting motor threshold. In each group, half of the subjects first performed the block in which the conditioning pulse intensity was set at 90%, while the other half were tested first with a conditioning intensity of 110%. In each block seven conditions were randomly intermingled: the test M1 pulse alone, or else combined conditioning pulse and test pulse at each of the six different ISI. Twenty responses were collected for the test stimulus alone and ten responses for paired conditioning and test pulses at each ISI, leading to 80 trials in total. The inter-trial interval was set at 4 s (±10%). Measurements were made on each individual trial with the mean peak-to-peak amplitude of the conditioned motor evoked potential then being expressed as a percentage of the mean peak-to-peak amplitude MEP for the unconditioned test pulse.

Experiment 2. Changes in left PPC-MI influences and in visual neglect after intervention with left PPC 1 Hz rTMS

In this experiment we compared possible changes in PPC-M1 influences for the LH before, versus one minute after, the application of a single session of 1 Hz rTMS trains. rTMS comprised 600 pulses in total over the left PPC for 10 patients from the neglect group and five from the no-neglect group. This rTMS protocol is known to induce an inhibitory effect on the stimulated area lasting ~15 min (Chen *et al.*, 1997) and has been reported to induce improvement in neglect symptoms when applied over the left PPC (Brighina *et al.*, 2003). The coil for rTMS was applied over the same site and with the same orientation as for the conditioning left PPC pulses in Experiment 1, and as repeated here for the twin-coil part of Experiment 2, see below. A MagStim Rapid magnetic stimulator (Magstim, Whitland, UK), connected with a figure-of-eight coil of diameter 70 mm, was used to deliver rTMS over the scalp site corresponding to left PPC. We repeated the twin-coil PPC-M1 procedure over the LH as in Experiment 1, both before and after the 1 Hz rTMS intervention in Experiment 2.

In the neglect group we also assessed visual neglect before and after the 1 Hz rTMS intervention, now using 20 visual chimeric objects each of which had to be named, with left neglect corresponding to failures in naming the identity of the half-object shown on the left of the chimeric, despite naming that on the right. The materials and protocol for this followed Sarri *et al.* (2006), albeit without their prism manipulation, substituted here by the 1 Hz rTMS over left PPC instead. We chose this specific chimerics task for several reasons. First, because it has been used in other recent studies of possible rehabilitation for neglect (Sarri *et al.*, 2006). Second, because unlike our left PPC-M1 TMS measure, the visual chimeric task is unlikely to involve hand-regions in left M1 specifically, so any improvement in chimeric neglect after rTMS would allow us to generalize beyond motor cortex. Third, most of the patients were undergoing extensive exposure to more common pen-and-paper assessments of neglect as part of their routine care. This precluded good experimental control over exposure to those measures, unlike for the new chimeric experimental measure introduced specifically for just this experiment. This evaluation was performed at least one week apart from the twin-coil PPC-M1 study.

Results

Experiment 1: hyperexcitability of left PPC-MI in neglect after RH damage

The lesion data are summarized in Fig. 1, for completeness. As apparent in the top-row of Fig. 1, the neglect group typically had substantial lesions centred on right perisylvian structures, similar to many previous studies of neglect. Also as expected, there was less overlap for the no-neglect group, shown in the bottom-row.

In the neglect group, resting motor threshold for left M1 (used to calibrate the intensity of the conditioning pulse over PPC for the twin-coil experiment) was 37.4 ± 7.8% of maximal stimulator output. The intensity of test stimulus over left M1 needed to produce a 1 mV motor evoked potential was 50.1 ± 11.8% of maximal stimulator output. The corresponding values for the no-neglect patient group were 36.3 ± 6.8%, and 48.3 ± 9.9% (Fig. 2). In the

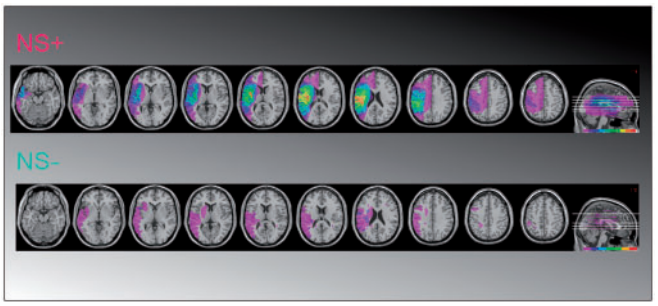

Fig. 1 Summary of lesions and overlap in our sample of RH stroke patients exhibiting symptoms of the neglect syndrone (NS+, top row) or those without neglect (NS−). The colour-scale at bottom-right of each row indicates the proportion of patients affected (higher for colours further to the right in the scale).

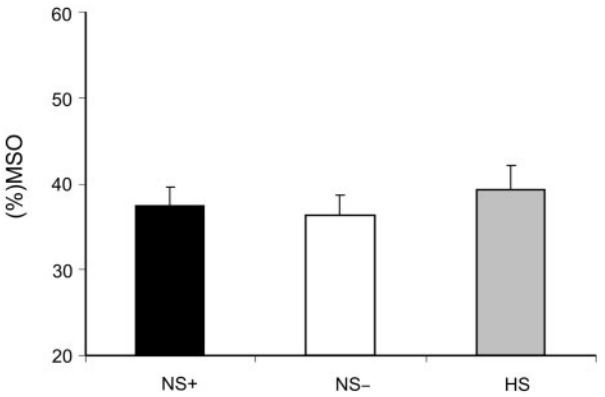

Fig. 2 Resting Motor Thresholds in the left motor cortex, shown here as percentage of maximal TMS stimulator output (MSO), did not differ between the two groups of patients (NS+ and NS−, black and white bars, respectively), nor as compared to the group of healthy subjects (HS, grey bar). Means and SEs shown.

age-matched healthy control group the values were 39.6 ± 7.8% and 49.2 ± 8.4% MSO. The procedure was tolerated well by all subjects.

Importantly, there were no significant differences between patient groups, nor against age-matched healthy controls, when comparing these basic motor 'threshold' measures (Fig. 2). This implies that excitability of motor cortex itself (left M1) was not pathologically increased for the intact contralesional hemisphere in the neglect group.

By contrast, the major new finding in Experiment 1 was that the strength of left PPC-MI functional influences did differ notably between neglect patients versus the no-neglect and healthy control groups (Fig. 3). The effects of paired TMS over left PPC, on the size of motor evoked potentials recorded from the right hand in response to left M1 TMS, were analysed as the percentage of the mean peak-to-peak amplitude of the unconditioned test M1 pulse. Mean percentage values were analysed in a mixed-design ANOVA, with 'group' as a between-subjects factor (neglect, no-neglect, or health controls), plus 'conditioning intensity' (110% or 90% of resting motor threshold) and the 'ISI' between left PPC and left M1 pulses (2, 4, 6, 8, 10 or 15 ms) as within-subjects factors.

In addition to main effects of group [$F(2, 27) = 4.1$, $P < 0.05$] and intensity [$F(1, 27) = 30.5$, $P < 0.001$], we found two-way interactions between group and intensity [$F(2, 27) = 3.3$, $P < 0.05$] and between intensity and ISI [$F(5, 135) = 2.92$, $P < 0.05$] (Fig. 3). *Post hoc* *t*-tests with Bonferroni correction compared the size of the left PPC-M1 influence between groups, for particular PPC intensities and PPC-M1 ISI. These showed that neglect patients, in comparison with the no-neglect patients, had stronger PPC-M1 facilitation for a conditioniong PPC intensity of 90% resting motor threshold, at ISI of 4 ms ($P < 0.05$), 8 ms ($P < 0.05$) and 10 ms ($P < 0.05$). The results were similar when comparing neglect patients against healthy controls instead: the neglect group had stronger facilitation for a conditioning PPC intensity of 90% resting motor threshold, that reached significance at ISI of 4 ms ($P < 0.05$), 6 ms ($P < 0.05$) and 10 ms ($P < 0.05$). The no-neglect and healthy-control groups did not differ. In both those groups the effects of PPC conditioning induced a peak facilitation of about 20%, as expected from our original PPC-M1 study in healthy controls (Koch *et al.*, 2007). Finally, there were no group differences at a PPC conditioning intensity of 110% (Fig. 3B).

Thus, in comparison with RH stroke patients without neglect, and with healthy controls, the neglect patients showed abnormally enhanced left PPC-M1 influences when the conditioning PPC intensity was 90% of resting motor thresholds (but not at higher intensity). This suggests that there is some hyper-excitability of 'left' PPC-M1 influences in 'right'-hemisphere-damaged patients with neglect (Fig. 3A).

Not all the neglect patients showed exactly the same degree of left PPC-M1 hyperexcitability. Further analyses revealed that the individual amount of facilitation induced by PPC conditioning (at 90% of resting motor threshold, for an ISI between PPC-M1 of 4 ms) in each neglect patient correlated with the severity of their clinical neglect, as revealed by the number of left sided omissions in line cancellation ($r = 0.69$; $P < 0.05$) or letter cancellation ($r = 0.63$; $P < 0.05$). Thus, patients who exhibited worse visuospatial neglect, on initial screening with pen-and-paper clinical cancellation tests, also tended to show stronger hyperexcitability of left PPC-M1 influences on the paired-pulse TMS measure (Fig. 4).

Experiment 2. Changes in PPC-MI influences following I Hz rTMS over left PPC

A 1 Hz rTMS protocol of 600 pulses was applied over the left PPC site of 10 patients from the neglect group and five

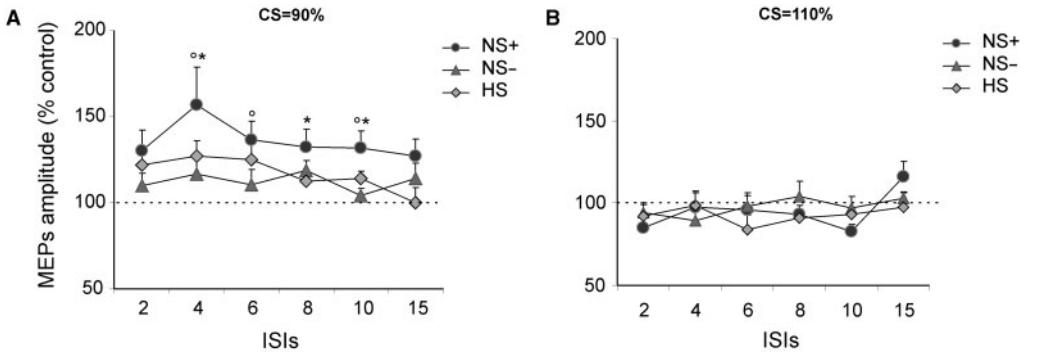

Fig. 3 A conditioning TMS stimulus (CS) was applied at either: (**A**) 90%; or (**B**) 110% of resting motor threshold over left PPC at a site corresponding to the inferior parietal lobe and angular gyrus near the caudal intraparietal sulcus. This CS was applied with different ISIs (shown across the x axis of each group) relative to a test stimulus pulse to left MI. The panels shows the left PPC-MI effects, relative to an MI pulse alone, obtained after PPC conditioning in the three different groups for Experiment I (neglect group = NS+; no-neglect group = NS−; healthy subjects = HS). The intensity of the test stimulus was fixed to evoke a motor evoked potential of ~1 mV peak-to-peak in the relaxed right first dorsal interosseous. Pathologically increased left PPC-MI effects were observed selectively in the neglect group at conditioning intensity of 90% (see left graph, **A**). Errors bars indicate SEM. Asterisk indicates significant differences in pairwise tests between NS+ and NS− groups; open cirlceindicates significant differences between NS+ and HS groups, all at $P < 0.05$ or better.

from the no-neglect group. The twin-coil PPC-M1 paradigm was applied both before and one minute after the 1Hz rTMS intervention, to allow a pre/post rTMS comparison.

The rTMS intervention significantly changed the left PPC-M1 effects only for the neglect group, and only at a conditioning intensity of 90% RMT (Fig. 5). This was confirmed by a mixed-design four-way ANOVA, with 'group' as a between-subjects factor (neglect, no-neglect), plus 'treatment condition' (before or after rTMS), 'conditioning intensity' during twin-coil TMS (90% or 110% or resting motor threshold), and PPC-M1 'ISI' (2, 4, 6, 8, 10 or 15 ms) as within-subject factors. In addition to main effects of conditioning intensity [$F(1, 9) = 18.6$, $P < 0.001$] and two-way interactions for group × treatment condition [$F(1, 13) = 3.3$, $P < 0.05$], group × intensity [$F(1, 13) = 7.2$, $P < 0.05$] and treatment × intensity [$F(1, 13) = 6.6$, $P < 0.05$], we also found a triple interaction [$F(1, 13) = 3.6$, $P < 0.05$]. Subsequent *post hoc* *t*-tests confirmed that the

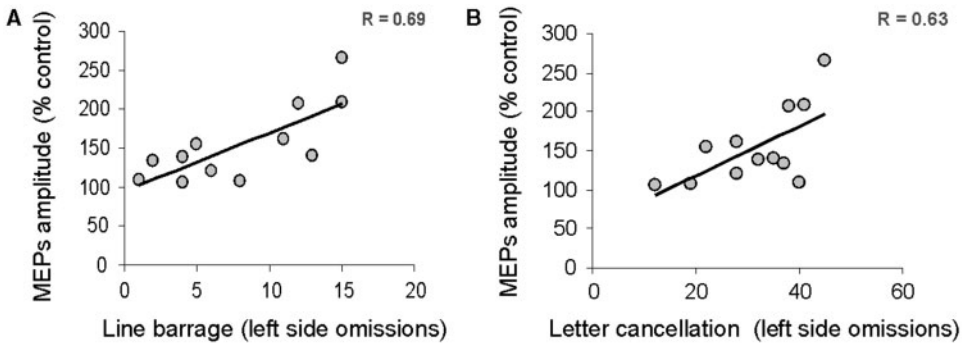

Fig. 4 In patients with neglect, the individual amount of facilitation induced by PPC conditioning at 90% intensity, for a PPC-MI interstimulus interval of 4 ms, correlated with severity of clinical neglect as exhibited by the number of left side omissions in (**A**) line cancellation ($r = 0.69$; $P < 0.05$); or (**B**) letter cancellation ($r = 0.63$; $P < 0.05$). Scatter plots illustrate this relationship, with linear regression line also shown. Thus, hyperexcitability of left PPC-MI influences as found with TMS tended to be larger in patients who showed worse visuospatial neglect as found with pen-and-paper cancellation measures.

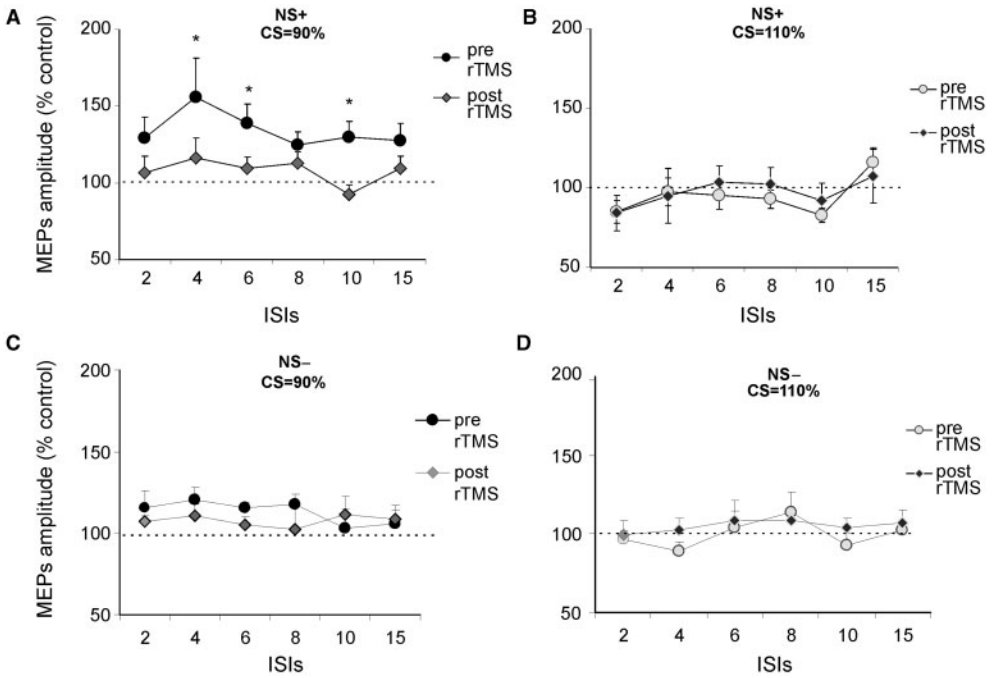

Fig. 5 The panel shows the changes induced by the left PPC 1 Hz rTMS intervention (600 stimuli at 90% of resting motor threshold) on the left PPC-MI connectivity effects. (**A**) The pathologically increased left PPC-MI effects observed in the neglect group (NS+) at a conditioning intensity of 90% prior to rTMS, as also found in Experiment 1 and Fig. 3A, were significantly reduced post rTMS in the NS+ group. Indeed, the neglect-specific pathology was now eliminated, with the NS+ group now becoming comparable to the NS− control group of patients. (**B**) No significant changes due to rTMS were detected in the neglect group at conditioning intensity of 110%. (**C** and **D**) rTMS did not change the normal pattern found in the non-neglect group (NS−) for either conditioning intensity. Errors bars indicate SEM; asterisk indicates *P*-value <0.05 in paired comparison of the two scores within each graph, at a given PPC-MI ISI.

size of the PPC-M1 effect was reduced after the 1 Hz rTMS treatment, only for the neglect group, and for them only with the conditioning intensity of 90%, and at the ISI of 2, 4, 6 and 10 ms (all $P < 0.05$); see Fig. 5A.

Positive effects of treatment were detected in 7 out of 10 individual neglect patients. Figure 6 shows for each neglect patient individually their left PPC-M1 effects (relative to the control baseline of just an M1 pulse without a preceding PPC conditioning pulse) for a conditioning PPC pulse of 90% intensity at an interstimulus-interval of 4 ms between PPC and M1. This is plotted separately for before (solid symbols) or after (empty symbols) the rTMS intervention.

At the group level, 1 Hz rTMS over left PPC effectively 'normalized' the hyper-excitability of left PPC-M1 influences in the neglect group, for a conditioning intensity of 90%. Direct comparison of the neglect and no-neglect groups 'after' the 1 Hz rTMS treatment had been applied over left PPC confirmed that these patient groups then no longer differed for left PPC-M1 effects (all P's non-significant).

Finally, we also found that the single session of 1 Hz rTMS over left PPC not only normalized the abnormal left PPC-M1 influences in the neglect group, but was also able to improve visuospatial neglect, as assessed with the experimental visual chimeric test taken from Sarri *et al.* (2006). A total of 79.5% (±7.5%) of the left-sides of the chimeric objects were not named prior to the 1 Hz rTMS treatment, but this improved to a reduced level of 65.6 ± 8.8% after the intervention ($P < 0.005$). Visual neglect was not completely eliminated, and the improvement on chimerics did not correlate with the individual size (Fig. 6) of the left PPC-M1 normalization revealed by the twin-coil TMS measure. As noted in discussion, the relationship might potentially be stronger for more motoric or 'intentional' aspects of neglect, a topic that might be addressed in future research. Nevertheless, our results clearly show that 1 Hz rTMS over left PPC has potential to normalize hyper-excitable influences within the LH, while also having some impact on visual neglect.

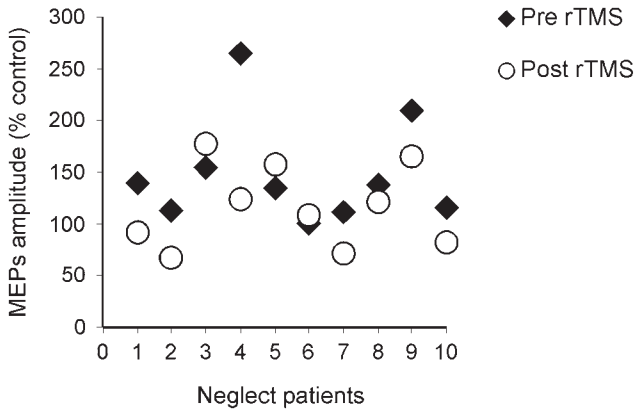

Fig. 6 In neglect patients, positive effects of the rTMS intervention upon the hyperexcitable left PPC-MI influences were detected individually in seven out of the 10 neglect patients who underwent rTMS. The graph shows for each neglect patient the individual peak of facilitation of left PPC-MI influences (relative to MI alone baseline) with PPC conditioning at 90% intensity and a PPC-MI ISI of 4 ms. This is shown separately prior to rTMS in Experiment 2 (solid symbols) and also after the 1 Hz rTMS intervention (empty symbols).

Discussion

The present findings used a new twin-coil TMS approach (Koch *et al.*, 2007, 2008) to show, for the first time, that even at rest the functional influence or inferred 'connection' between left PPC-M1 is hyperexcitable in RH patients with neglect, compared with RH patients without neglect, or healthy age matched controls. This provides a new and highly direct form of physiological evidence for 'hemispheric-rivalry' notions that some circuits in the LH may become disinhibited in RH neglect patients, presumably due to release from mutual inhibition due to the particular RH lesion of the neglect group. We note that left M1 in itself did not seem hyper-excitable in the neglect group (Fig. 2), but rather it was the specific impact of left PPC upon left M1 that became pathologically exaggerated (Fig. 3). This indicates that rather than the LH as a whole becoming more excitable, specific influences from left PPC do so, presumably due to right PPC damage. Particular lesions in the right hemisphere may induce changes in the cortico-cortical excitability of corresponding specific areas and circuits in the non-lesioned hemisphere, through a mechanism of locally reduced transcallosal inhibition.

As a further means of demonstrating the crucial role of 'left' PPC in patients with RH damage, in a follow-up study (Experiment 2), we applied inhibitory 1 Hz rTMS over this side. In confirmation of previous work (indicating that this intervention may have potential for improving symptoms of neglect (Brighina *et al.*, 2003), we found that visual neglect for chimeric objects could be partially but significantly ameliorated after 1 Hz rTMS. But more specifically, we also found that the 1 Hz rTMS intervention normalized the hyper-excitability of left PPC-MI influences for the neglect group, indicating that such rTMS provides an effective means for eliminating over-excitability in LH circuits.

With recent experiments in normals (Koch *et al.*, 2007, 2008), we demonstrated that PPC-M1 influences are enhanced during action planning of reaches in the contralateral direction. Invasive electrophysiological studies in monkeys have also suggested roles for PPC in converting target locations into motor intentions (see Cohen and Andersen, 2002 for review; see also Cavada and Goldman-Rakic, 1989; Seltzer and Pandya, 1994; Johnson *et al.*, 1996). Moreover, parietal regions may over-represent contralateral workspace relative to ipsilateral workspace

(Battaglia-Mayer *et al.*, 2005). It has been suggested that, in humans, damage to such parietal representations might explain some directional aspects of intentional or motor-related neglect (e.g. directional hypokinesia). This may include right parietal patients being impaired at initiating reaches in the leftward direction, over and above any visual or attentional impairments for left targets (Heilman *et al.*, 1985; Mattingley *et al.*, 1998; Husain *et al.*, 2000). In the light of this growing body of literature, the present hyper-excitability of parieto-motor influences that we found in the intact LH may contribute to the skewed spatiomotor behaviour that is so evident in neglect patients. In this respect, it may be informative in future work to assess how the twin-coil PPC-M1 abnormalities for the LH in neglect patients may relate specifically to spatiomotor aspects of their clinical disorder (Heilman *et al.*, 1985; Mattingley *et al.*, 1998; Husain *et al.*, 2000), rather than just to visual aspects of neglect, as was assessed here with the chimeric objects.

Finally, we found that inhibitory low frequency 1 Hz rTMS applied over left PPC could attenuate the pathological over-excitability of parieto-motor circuits in neglect patients, as assessed with our new paired-pulse PPC-M1 TMS measure. Such 1 Hz rTMS has also been shown to ameliorate clinical aspects of neglect-related behaviours (Brighina *et al.*, 2003), as we also found here for visual chimerics. Taken together, our findings provide a new and direct form of physiological evidence for the idea (Kinsbourne, 1993; Oliveri *et al.*, 1999) that unbalanced excitability of the two hemispheres, is an important contributor to neglect, with hyper-excitability arising for some specific LH circuits. We suggest that not only is damage in the extensive right-lateralized, attention-related network an essential contributor to neglect (Mesulam, 1981; Corbetta *et al.*, 2005; Thiebaut de Schotten *et al.*, 2005; He *et al.*, 2007), but also that consequent hyper-excitability of particular circuits in the intact hemisphere may make further contributions. In this regard, it is important to notice that the present experiments only address one out of many possible connections between parietal and more anterior areas (here M1) in the non-lesioned hemisphere. Others could potentially be examined using combined TMS-EEG or combined TMS-fMRI methods, in addition to methods that can trace anatomical connectivity such as Diffusion Tensor Imaging. In such ways, future extensions of our work may further define the hypothesis of contralesional hyper-excitability, and delimit exactly which circuits are associated with the observed neurophysiological changes.

In conclusion, our results provide direct new evidence that abnormal excitability of cortical networks in the unaffected hemisphere can be an important contributor to neglect. They also reinforce the idea that interventional approaches directed to ameliorating this imbalance may be useful in treating neglect symptoms.

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