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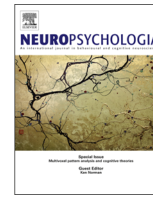

Research report

Contralesional rTMS relieves visual extinction in chronic stroke

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ABSTRACT

Patients affected by right parietal lobe lesion can be severely impaired in sustained attention tasks, particularly in the left visual field. For example, patients with right parietal stroke are commonly limited in their ability to attentionally track multiple moving objects in their left visual field when competing stimuli are simultaneously presented in the right, ipsilesional visual field. This is a hallmark of visual extinction, a failure to respond to contralesional visual stimuli, when competing stimuli are presented in the good hemifield. It has been hypothesized that post-stroke hyperactivity of the undamaged left hemisphere leads to excessive cross-hemispheric inhibition of the damaged right hemisphere, thus exacerbating the attentional deficits. However, there has been no direct physiological demonstration of this hypothesis, as most of the studies are conducted using unilateral tasks, a condition not sufficient to drive inter-hemispheric competition. The inter-hemispheric inhibition hypothesis also raises the possibility that if hyperactivity of the healthy hemisphere was reduced, this could relieve inter-hemispheric inhibition, disinhibiting the damaged hemisphere and potentially restoring some function. To test this hypothesis, and to examine whether we could relieve deficits in sustained attention in right parietal patients, we used repetitive transcranial magnetic stimulation (rTMS) to reduce the activity of the left, healthy hemisphere. Six patients suffering from visual extinction underwent two counter-balanced sessions: low frequency rTMS over the left parietal lobe and sham control stimulation. The patients' performance in an attentional tracking task significantly improved in the contralesional visual field immediately after rTMS, but not after sham. Performance remained unaltered in the ipsilesional field. We hypothesize that rTMS temporarily releases the damaged right hemisphere from excessive cross-hemispheric inhibition by the hyperactive healthy hemisphere, leading to some cognitive recovery after cortical lesion.

1. Introduction

Patients with a right parietal lesion show severe impairments in visual attention. Visual hemispatial neglect is the classical behavioral deficit after right parietal lesion. While visual neglect commonly involves ventral cortical areas such as the temporo-parietal junction and the superior temporal sulcus (Vallar & Perani, 1987; Mort et al., 2003; Karnath & Rorden, 2012), damage in these areas is also associated with functional impairment of the intra-parietal sulcus (IPS) and the superior parietal lobule, that otherwise appears to be structurally normal (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005).

The classic "pencil and paper" clinical findings in the acute phase after parietal stroke is hemispatial neglect, characterized by the failure to attend, search, and respond to stimuli presented to the contralesional visual field (Critchley, 1953), without concurrent sensory deficits (Vallar et al., 1991). However, in the chronic phase, patients show less overt neglect, but commonly show signs of visual extinction, an inability to detect a contralesional stimulus when an ipsilesional stimulus is simultaneously presented (Wortis, Bender, & Teuber, 1948). The notion of the co-occurrence of the two symptoms has been challenged by recent findings (Umarova et al., 2011; Vuilleumer & Rafal, 2000), showing that visual extinction and neglect are dissociable syndromes, although both deficits are commonly associated with right hemisphere lesions (Stone, Halligan, & Greenwood, 1993; Vossel et al., 2011; Corbetta & Shulman, 2011). Additional deficits can be difficult to measure with standard clinical testing, but can persist in the chronic phase. For instance, psychophysical studies

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have shown that chronic right parietal patients are still severely impaired in attention-based computations, both in the spatial (Battelli et al., 2001) and temporal domains (Battelli, Cavanagh, Martini, & Barton, 2003; Arend, Rafal, & Ward, 2011). In particular, visual tracking of moving objects is one aspect of attention poorly studied in parietal patients, and typically involving sustained attention, a well studied behavioral paradigm with clear neural correlates (Drew & Vogel, 2008; Culham et al., 1998; Battelli et al., 2001). This task should not be confused with vigilance tasks, usually designed to measure the level of alertness in traumatic brain patients (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), but with poor sensitivity to measure performance across hemifields.

Different models have been proposed to explain this right-hemisphere specialization for attentional functions. A leading model, based on patients' studies, holds that the right hemisphere directs attention to both hemifields, while the left hemisphere orients attention only toward the contralateral hemifield (Mesulam, 1981). Thus a lesion in the left hemisphere has a lower chance of causing visuospatial deficits because attentional functions are compensated for the right hemisphere, while a right hemisphere lesion results in a deficit in the left visual field, since the left hemisphere cannot compensate for the left visual field deficit.

Kinsbourne (1977) proposed an alternative explanation for visual neglect and extinction, based on a rivalry or competition between hemispheres. The author studied bias in orienting attention using a line-bisection task (Kinsbourne, 1977). Participants were asked to judge the relative length of the two resulting segments of a horizontal line divided by a perpendicular intersect. Results indicated that the distribution of spatial attention is biased in the controlateral direction to the activated hemisphere. However, the bias resulting from the left hemisphere (right hemifield) was more robust than that resulting from the right hemisphere (left hemifield) (Kinsbourne, 1977). The author concluded that homologous cortical areas within each hemisphere normally direct attention to the contralateral visual field, but also exert reciprocal inhibition via reciprocal transcallosal connections to keep a balanced distribution of attention across the visual field (Oliveri et al., 1999; Cazzoli, Müri, Hess, & Nyffeler, 2010). If this balance is disrupted following a unilateral stroke, the attentional system could be biased toward the ipsilesional visual hemifield. In this view, right hemisphere damage results in the disinhibition of the left hemisphere. As a consequence, the strong rightward orienting tendency of the left hemisphere is unopposed and produces the classical visuospatial deficit. In contrast, after left hemisphere damage, the leftward bias of the right hemisphere is inherently weaker, leading to a less severe directional bias.

In fact, there is recent evidence consistent with the inter-hemispheric competition hypothesis. For example, inhibitory transcranial magnetic stimulation (TMS) over right, but not left posterior parietal cortex induces a neglect-like rightward bias (Hilgetag, Theoret, & Pascual-Leone, 2001; Dambeck et al., 2006; Bien, ten Oever, Goebel, & Sack, 2012). Interestingly, this neglect effect could be reversed by subsequently stimulating left parietal cortex (Cazzoli et al., 2010), potentially due to restoration of the normal interhemispheric balance mediated by transcallosal pathways (Kinsbourne, 1977; Koch et al., 2011).

There is also functional imaging evidence consistent with inter-hemispheric competition (Corbetta et al., 2005; Dambeck et al., 2006). Corbetta and colleagues found that the "undamaged" right superior parietal lobule is hypoactive in patients with a right hemisphere lesion suffering from left visual neglect, while the homologous area in the left hemisphere is hyperactive (Corbetta et al., 2005; Corbetta & Shulman, 2011). In these studies the patients' strokes were in a right-lateralized ventral network that includes the temporo-parietal junction and the ventral frontal cortex; however, that ventral network is believed to be functionally connected to the right dorsal parietal attentional network, such that a damage in the right ventral network would also compromise functions of the right dorsal parietal network (Corbetta & Shulman, 2002, 2011).

An important implication of these studies is that hyperactivity in the left, healthy hemisphere could lead to hypoactivity in the damaged right hemisphere, preventing the full recovery of attentional functions mediated by the right hemisphere (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). We therefore hypothesized that if the hyperactivity of the left hemisphere could be reduced in some manner, it could relieve excessive inhibition of the damaged right hemisphere and promote the functional recovery of the right hemisphere. In fact, previous studies have provided some evidence that inhibition of the left hemisphere with repetitive transcranial magnetic stimulation (rTMS) could lead to some recovery of right hemisphere function in affected patients (Oliveri et al., 1999; Brighina et al., 2003; Koch et al., 2008; see Müri et al. (2013) for a review). However, none of these studies used TMS to relieve symptoms of visual extinction that persist in chronic stroke. Q6

Here, we used 1-Hz inhibitory rTMS to reduce the activity of the intact left hemisphere in right parietal stroke patients, so as to "re-balance" the activity between homologous left and right parietal areas. We examined the patients' accuracy in a sustained attention tracking task, which is strongly impaired in right parietal patients (Battelli et al., 2001). At baseline, patients showed the classical unilateral (contralesional) spatial deficit during bilateral tracking only, a form of spatial extinction (Battelli et al., 2001). However, the patients' performance improved significantly after 1-Hz inhibitory rTMS over the healthy left parietal cortex. The improvement was selective for the impaired hemifield. Interestingly, the effect extended in time beyond the actual rTMS procedure, reaching peak effect 30 min after the end of stimulation. These findings suggest a potential therapeutic approach for attentional deficits following stroke, specifically for those deficits that might go undetected but can still be the underlying cause of the inability to achieve full recovery in chronic stroke.

2. Methods

2.1. Case histories

We tested six patients with right hemisphere lesions. They all had a unilateral lesion due to a cerebrovascular stroke, confirmed by radiological examination (CT or MR). None had any history or evidence of degenerative disease or psychiatric disorder. All participants were right-handed, native Italian speakers, and had normal or corrected-to-normal visual acuity (see Table 1 for demographic and lesion-site data). Patients were tested in their chronic stage after the stroke, at least 6 months post-onset.

Patient AC, a 72-year-old right-handed man, had an ischemic stroke in December 2009. CT scan showed ischemic damage to right frontal, insular and parietal regions (including the supramarginal gyrus), with involvement of the temporal pole and partial involvement of the upper surface of the superior temporal gyrus. A neuropsychological evaluation performed in 2011 showed mild signs of visuospatial neglect.

Patient BM, a 51-year-old right-handed woman, had a stroke in October 2011. CT scan showed a large ischemic lesion in the region of the right middle cerebral artery. The neuropsychological evaluation performed in November 2011 showed visual and tactile extinction.

Patient FA, a 70-years-old right-handed man, had a stroke in August 2011. His CT scan showed a right capsulo-thalamic hemorrhage also involving the temporal regions. The neuropsychological evaluation performed at the hospital showed tactile extinction.

Patient GL, a 79-years-old right-handed man, had a stroke in September 2009. His CT scan showed signs of a hemorrhagic stroke, confirmed by a follow up MRI. GL had a massive ischemic lesion involving the regions of the right middle cerebral artery. The neuropsychological evaluation performed immediately after the stroke showed left hemispatial neglect.

Patient RR, a 67-year-old right-handed man, suffered a right parietal lobe focal ischemia in 2011. At the first neuropsychological evaluation 4 months post-onset he presented with symptoms of left hemispatial neglect that gradually recovered. The

Table 1
Demographic and lesion data. All right parietal patients had a unilateral stroke due to cerebrovascular lesion. Symptoms described in the table refer to the neuropsychological evaluation carried out at the hospitals after the lesion using the Behavioral Inattention Test (Halligan, Cockburn, & Wilson, 1991). The fourth column indicates the time from onset at which we tested them.

Patient	D.O.B.	Symptoms	Lesion	Time from onset (months)
A.C.	10/01/1939	Mild left visual neglect	Right middle cerebral artery ischemic stroke (fronto-temporo-parietal lesion)	23
B.M.	29/11/1961	Left visual and tactile extinction	Right middle cerebral artery stroke	8
F.A.	27/01/1943	Left tactile extinction	Right capsulo-thalamic hemorrhagic stroke	16
G.L.	13/05/1933	Left neglect	Right middle cerebral artery stroke	33
R.R.	24/04/1944	Extrapersonal, peripersonal and personal left neglect	Right ischemic stroke involving cortical and subcortical areas	8
T.E.	12/06/1946	Left visual and tactile extinction	Right middle cerebral artery ischemic stroke	13

MRI showed a diffuse damage to the frontal and (mostly) parietal white matter of the right hemisphere, lateral and superior to the lateral ventricle. There was patchy cortical and subcortical damage on banks of the intraparietal sulcus. Most lesions were located in the superior parietal lobule; some lesions were in the inferior parietal lobule.

Patient TE, a 68-year-old right-handed woman, suffered a stroke in May 2011. She had a massive, superficial and deep ischemic damage to right frontal, insular and parietal regions (including the angular and supramarginal gyrus and the inferior parietal lobule), with involvement of the temporal pole and of the upper surface of the superior temporal gyrus. The neuropsychological evaluations performed in August 2011 and then in October 2011 showed left visual neglect that gradually recovered. A further neuropsychological evaluation performed 9 months post-onset revealed signs of visual and tactile extinction on double simultaneous stimulation.

All patients showed visual extinction in the left hemifield during bilateral tracking, when tested on the multiple objects tracking task (see Section 3.2 of the results).

They gave informed consent before participating in the study, according to the ethical standards of the Declaration of Helsinki. The study was approved by the ethical committee of the University of Trento and of the Carlo Poma Hospital. Patients were recruited and tested at the Center for Neurocognitive Rehabilitation (CeRiN) affiliated to the University of Trento and the Rehabilitation Department of the Carlo Poma Hospital, in Mantua, Italy. Three patients with left parietal lesion, with no sign of visual neglect or extinction, (3 males, average age=52 yrs) and six age-matched ($t_{(10)}=0.92$, $p<0.38$) neurologically unimpaired subjects (4 males, average age=65 yrs) also participated in the study. The left parietal patients and the unimpaired subjects underwent behavioral testing only.

2.2. Materials and procedure

2.2.1. Stimuli

Subjects were tested with a multiple object tracking task. The task was presented on a MacBook Pro laptop using running software based on the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) in Matlab (MathWorks). The visual displays consisted of a central fixation point (a black circle, radius=0.15°) and eight moving black circles (radius=0.3°) presented on a gray background. Four circles moved within a 6°×6° region inset, centered 2° to the left and right of fixation. Items moved at a constant speed, repelled each other to maintain a minimum center-to-center spacing of 1.5° and "bounced" off of the invisible edges of the square region in which they moved (for more details see Battelli, Alvarez, Carlson, and Pascual-Leone (2009)).

2.2.2. Speed threshold

On the first day of testing, subjects were all tested for baseline functions. Two tasks were randomly interleaved, a unilateral and a bilateral tracking task. The speed of the moving circles was adjusted to control the difficulty of the task: trials with faster moving circles were more difficult. Importantly, to equalize task difficulty between the unilateral and the bilateral conditions, for each subject we psychophysically determined the speed threshold at which subjects could perform the task at 75% accuracy. At the beginning of each trial, the fixation point was presented for 1 s, then eight circles appeared (4 on the left, 4 on the right), and a subset blinked off and on at 2 Hz for 3 s to identify those circles as the targets for tracking. In the unilateral condition two circles, either on the right or the left visual field, blinked; in the bilateral tracking condition four circles, two on the right and two on the left, blinked on and off. After blinking, all the circles moved without crossing the midline for 3 s. After the movement ended, one of the circles was highlighted in red, with an equal probability that the highlighted circle was a target to-be-tracked or a distractor. The subject was then asked to say whether the red item was a target or not, with a response time cutoff of 10 s. An experimenter, blind to whether the subject had or had not received real TMS (see next section), recorded patients' answers by pressing one of two keys on the keyboard. To provide feedback to the subject, the fixation point turned green for a correct response or red for an incorrect response. The next trial began immediately following this feedback (Fig. 1).

Subjects first completed a practice block (16 trials) in which the circles moved at 2°/s. Four test blocks ensued, in which circles moved at one of eight different speeds (speeds were individually set for each subject) on each trial, with speeds randomly interleaved over 4 blocks of 32 trials each. This threshold procedure was used to identify the speed at which two (unilateral condition) or four targets (bilateral condition) could be tracked with 75% accuracy. Different speed thresholds were obtained for each subject, and separate thresholds were computed for the unilateral and the bilateral conditions.

2.2.3. TMS protocol

TMS pulses were delivered using a 70 mm figure-8-coil connected to a Magstim Rapid^2 (Magstim Co., UK). Each patient with right parietal lesion was submitted to two stimulation sessions separated by at least 24 h: 1-Hz active rTMS or sham stimulation over the intact left parietal cortex. The order of TMS or sham stimulation was counterbalanced across subjects. In the active TMS session we applied a 10-min train of repetitive low-frequency (1 Hz) stimulation over P3, identified using the 10/20 EEG measurement system. Stimulation strength was set to 90% of the threshold to evoke motor responses at rest (Koch et al., 2008 and see below). To aid in brain-site localization, subjects wore a Lycra swimmer's cap on which the reference point for stimulation was marked. In three patients we verified proper measurements using a custom designed EEG cap with the P3 site already marked on the cap. For the active stimulation condition, the coil was held with the handle pointing backward toward the back of the head and was positioned perpendicularly to the stimulated region, for sham stimulation, the coil was oriented perpendicular to the scalp, with the border of one wing placed against the subject's scalp.

During each TMS session patients performed the task three times: before rTMS, immediately after rTMS and 30 min from the end of stimulation. A preliminary psychophysical measurement, on a different day, was run to determine the speed threshold for the unilateral and the bilateral conditions (see above). The speeds were then kept constant throughout the entire rTMS experiment and accuracy was measured for each of the three measurements (baseline, immediately after rTMS and 30-min post-rTMS). We ran 48 trials, 12 for each condition (unilateral vs. bilateral, left and right visual fields) at the speeds (unilateral vs. bilateral) individually calculated, resulting from the patients' combined performance in both hemifields. The time required to perform the psychophysical task (10–12 min) is within the range for which offline rTMS in parietal regions has been shown to have Q7
lasting effects (Battelli et al., 2009; Hilgetag et al., 2001).

2.2.4. Motor threshold

We measured the motor threshold for each right parietal patient on the first day of testing. This was done to determine the intensity of stimulation for the parietal cortex. MEPs induced by single-pulse TMS were recorded from the first right dorsal interosseus (FDI; in the region between the thumb and index finger) using a Powerlab 4/30 system (ADInstruments, Oxford, United Kingdom). MEPs were recorded using a pair of Ag/AgCl surface electrodes (6 mm diameter). The ground electrode was placed on the participant's wrist. The EMG signal was band-pass filtered (10–1000 HZ) at a sampling rate fixed at 4 kHz. Data were digitized and stored on a Macintosh MacBook Pro computer (Apple Computers, Cupertino, CA, USA) for off-line analyses. The TMS coil was placed over the left M1. The resting motor threshold and the optimal hotspot were defined as the minimum TMS intensity necessary to elicit MEPs of >50 mV peak-to-peak amplitude in 5 of 10

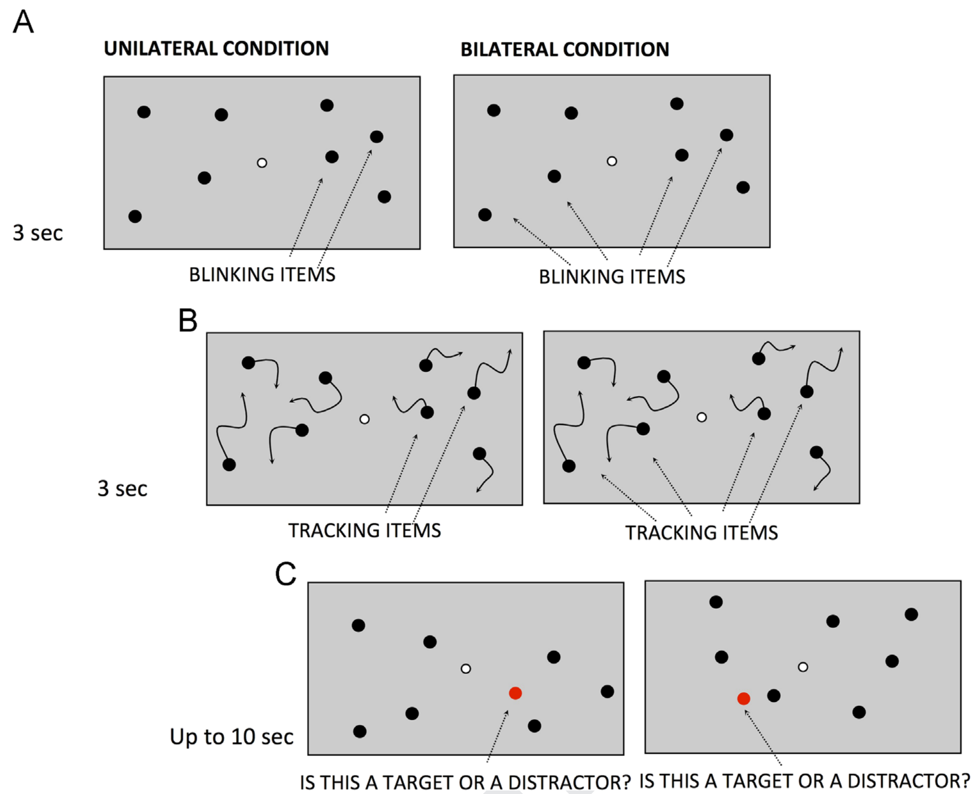

Fig. 1. Visual tracking task A) The stimuli consisted of eight moving circles, four positioned to the left and four to the right of a central fixation. At the beginning of each trial a subset of circles started to blink on-and-off (unilateral tracking condition: either two on the left or two on the right visual field; bilateral tracking condition: two on the left and two on the right visual field) to identify them as targets for tracking. B) After blinking, all the circles moved for 3 s. C) After all items stopped, one of the circles was highlighted in red for target/distractor discrimination.

consecutive trials (Rossini et al., 1994) in the contralateral first right dorsal interosseus.

2.2.5. Data analysis

To quantify the effect of parietal lesions psychophysically, we first measured baseline psychophysical speed thresholds in the attentional tracking task before the TMS sessions, for the right parietal patients ($n=6$), left parietal patients ($n=3$) and age-matched control subjects ($n=6$). Speed thresholds were measured separately for the unilateral and bilateral tracking tasks. We calculated a combined threshold obtained from both visual fields' speed threshold to highlight left vs. right visual field differences in accuracy.

After we determined speed thresholds, we measured patients' performance at fixed (threshold) speed. For the right parietal patients, our hypothesis was that rTMS over the left, unaffected hemisphere would relieve inhibition of the lesioned right hemisphere, and therefore improve attentional performance in the left visual hemifield. Ideally, one would perform rTMS and then re-assess the speed thresholds for the attentional task; however, because finding the speed threshold is time-consuming, we were concerned that there would not be sufficient time before the effects of rTMS would wear off. For this reason we chose to compare pre and post-stimulation accuracy at fixed speed. Because the speed threshold in the bilateral task was calculated using both left and right visual field trials, by definition, the averaged speed was generally above threshold for the left (affected) hemifield and below threshold for the right (unaffected) hemifield. We expected to find a significant difference in right parietal patients' accuracy between the two hemispheres, with lower accuracy in the left visual field.

Speed threshold and baseline accuracy at threshold were measured for all three group of subjects, while only right parietal patients underwent post-stimulation testing. We stimulated the patients at an average intensity of 57% of the maximum stimulator output (range=45–64%), with intensity determined by the preliminary motor-threshold measurement (see Section 2).

To highlight the effect of stimulation, pre-TMS performance (% correct trials) was subtracted from the post-TMS performance, so that positive numbers indicated improvements in performance after stimulation and negative numbers indicated impairment after stimulation.

Data were compared using ANOVAs and Bonferroni-corrected *t*-tests. Finally, we calculated the effect sizes for the ANOVA and the *t*-tests comparison (Lakens, 2013).

3. Results

3.1. Baseline psychophysical speed thresholds

A mixed ANOVA was run with *task* (unilateral vs. bilateral) as within-subject factor and *group* (right parietal patients vs. left parietal patients vs. age-matched control subjects) as between-subject factor. As expected, unilateral and bilateral speed thresholds were significantly different ($F_{(1,12)}=34.29$, $p<0.001$, $\eta^2=0.70$), with a higher speed threshold in the unilateral condition for all three groups (Fig. 2). A higher speed threshold in this case means that the performance was better. The factor *group* was significant ($F_{(2)}=9.73$, $p=0.003$, $\eta^2=0.62$) (Fig. 3), with a Dunnett post-hoc test indicating a significant difference between thresholds for right parietal patients and age-matched control subjects ($p<0.003$) but no difference between left parietal patients and control subjects ($p=0.998$). The interaction task∗group did not reach significance ($F_{(2,12)}=1.06$, $p=0.376$, $\eta^2=0.04$).

3.2. Pre-TMS performance

We first ran two separate ANOVAs (using % correct trials) for the unilateral and bilateral tasks, with pre-stimulation baselines (pre-rTMS vs. pre-sham) and visual field (right vs. left) as within-subjects factors. For the bilateral task, we found a main effect of visual field ($F_{(1,5)}=6.6$, $p=0.05$, $\eta^2=0.48$), with lower accuracy in the left visual field (55%) than in the right field (74%). No significant effects were found in the unilateral condition ANOVA (Fig. 3A). For comparison, we also analyzed performance of the age-matched control group, and we did not find significant difference in performance between left and right visual fields in either the unilateral ($p=0.856$) or bilateral task ($p=0.999$) (Fig. 3B).

As expected, we found a significant difference in performance between the left and right visual fields during bilateral tracking only, with worse tracking accuracy in the left visual hemifield than the right visual hemifield, a signature of visual extinction upon double simultaneous presentation (Battelli et al., 2001).

3.3. Effects of TMS

Once we verified that right parietal patients had a deficit in sustained attention in the bilateral tracking task, we proceeded with the TMS session.

A repeated measures ANOVA was run with *stimulation* (active vs. sham), *task* (unilateral vs. bilateral), *session* (immediately post-rTMS vs. 30 min post-rTMS) and *visual field presentation of the target* (left vs. right visual field) as within-subjects factors. The ANOVA showed a main effect of stimulation ($F_{(1,5)}=9.54$, $p=0.027$, $\eta^2=0.09$) indicating a significant improvement after active but not after sham stimulation and a significant stimulation*task interaction ($F_{(1,5)}=9.94$, $p=0.025$, $\eta^2=0.03$) indicating a bigger improvement in the unilateral task than the bilateral task after active stimulation relative to sham ($t_{(5)}=3.87$, $p=0.012$, $g_{rm}=1.76$). The ANOVA also revealed a significant stimulation*task*visual field interaction ($F_{(1,5)}=16.73$, $p=0.009$, $\eta^2=0.02$). To measure whether there were any differences between active and sham stimulations in the unilateral and bilateral conditions for both visual fields, we performed four post-hoc paired *t*-test comparisons, corrected for multiple comparisons using the Bonferroni method (corrected alpha of 0.0125). Post-hoc *t*-tests indicated an improvement in the unilateral ($t_{(5)}=8.06$, $p<0.001$, $g_{rm}=1.30$) and bilateral ($t_{(5)}=4.15$, $p=0.009$, $g_{rm}=0.84$) conditions in the left visual field after active compared to sham stimulation (Fig. 4). No improvement was detected for the right visual field. Patients' individual data are shown in Fig. 5.

In the ANOVA, the interaction stimulation*task*session also tended to significance ($F_{(1,5)}=5.48$, $p=0.066$, $\eta^2=0.01$). To further examine the time-course of the post-rTMS effects, we performed four post-hoc paired *t*-tests comparing the immediately-post-rTMS and the 30 min-post-rTMS conditions in the unilateral and bilateral tasks for the active stimulation and sham (Bonferroni corrected with $\alpha=0.0125$). None of the post-hoc *t*-test reached significance. The difference between the immediately-post-rTMS and the 30 min-post-rTMS conditions for the active stimulation in the bilateral condition was not significant (Bonferroni corrected, $t_{(5)}=-3.53$, $p=0.017$, $g_{rm}=1.66$). However, it is evident in Fig. 4 that the effect that drove the significance is clearly, at 30 min after rTMS.

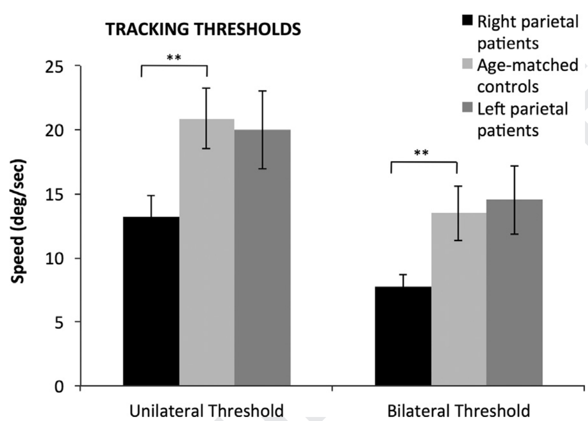

Fig. 2. Speed threshold. Tracking thresholds for right-parietal patients (black bars), age-matched controls (light gray bars) and left-parietal patients (dark gray bars). Right parietal patients' thresholds are significantly lower relative to age-matched controls in both tracking conditions, unilateral and bilateral. No difference was found between left-parietal patients and age-matched controls. **Asterisks indicate significant difference.

4. Discussion

We found that low-frequency inhibitory rTMS over the *intact* left parietal cortex improved sustained attention in the left visual field—contralateral to the lesion—in patients with right parietal damage. This improvement was present for both the unilateral (tracking within one visual field) and the bilateral tasks (tracking in both visual fields simultaneously).

Importantly, the effect was selective for the left visual field: we did not detect an effect in the right visual field. This indicates that TMS did not exert a non-specific effect on performance, but rather promoted a selective improvement of the damaged functions for bilateral tracking as well as an enhancement of unilateral tracking, all within the left hemifield. We also found no effect of sham stimulation, which further controls for possible generic effects of TMS not specifically related to active stimulation.

Our results support Corbetta and Shulman's model (2002, 2011) of unbalanced activity between the two hemispheres as a consequence of a unilateral stroke. While Corbetta et al. (2005) showed this functionally in an fMRI study by showing loss of balance between hemispheres that correlated with impaired performance in right parietal patients, we infer an imbalance between the two hemispheres by the fact that we could relieve the attentional deficits by directly lowering the activity of the unimpaired hemisphere using rTMS.

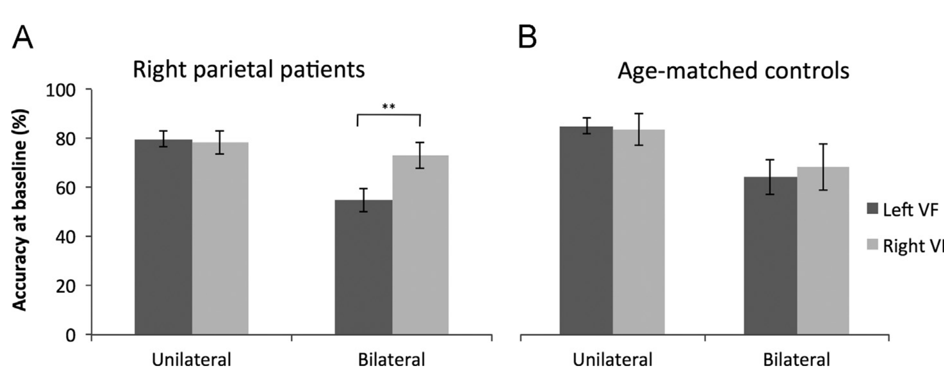

Fig. 3. Baseline accuracy. Average percent accuracy at baseline in the unilateral and bilateral tracking conditions. A) Only right-parietal patients show a significant difference between left (dark gray bars) and right (light gray bars) visual field accuracy in the bilateral tracking condition, indicating impaired performance. **Asterisks indicate significant difference. B) Average percent accuracy for 6 age-matched control subjects for the unilateral and bilateral conditions.

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We suggest that the specific improvement we observed is due to rTMS inhibiting activity in the left (intact) hemisphere, leading to a temporary re-balancing of activity between the two hemispheres. Right hemisphere hypoactivation after a right lesion and concurrent left hemisphere hyperactivation have been observed by functional imaging (Corbetta & Shulman, 2011; Corbetta et al., 2005) and by rTMS applied over the motor cortex (Koch et al., 2011). We therefore hypothesize that reducing hyperactivation of the healthy hemisphere results in a temporary recovery of the interhemispheric balance, leading to improved behavioral performance.

Previous studies have used TMS to relieve the behavioral deficits that follow right parietal lesion in acute stroke patients (Oliveri et al., 1999, 2001; Shindo et al., 2006; Nyffeler, Cazzoli, Hess, & Muri, 2009; Song et al., 2009; Cazzoli et al., 2012). Oliveri et al. (1999) showed reduced tactile extinction and visual neglect after stimulation of the left hemisphere in right parietal patients. The same authors (Oliveri et al., 2001) as well as Brighina et al. (2003) found rTMS over the left parietal cortex reduced contralesional neglect, as measured by performance in paper-and-pencil tests like line-bisection, clock-drawing and line cancellation. Finally, Nyffeler et al. (2009) and Koch et al. (2012) found that theta burst stimulation over the left parietal cortex improved performance in a visual detection task and in the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987). Therefore, while the improvement we found in the unilateral condition is not entirely surprising given the studies mentioned above, however, to the best of our knowledge, none of the previous studies on parietal patients have caused a large reduction of visual extinction in chronic stroke using low frequency rTMS.

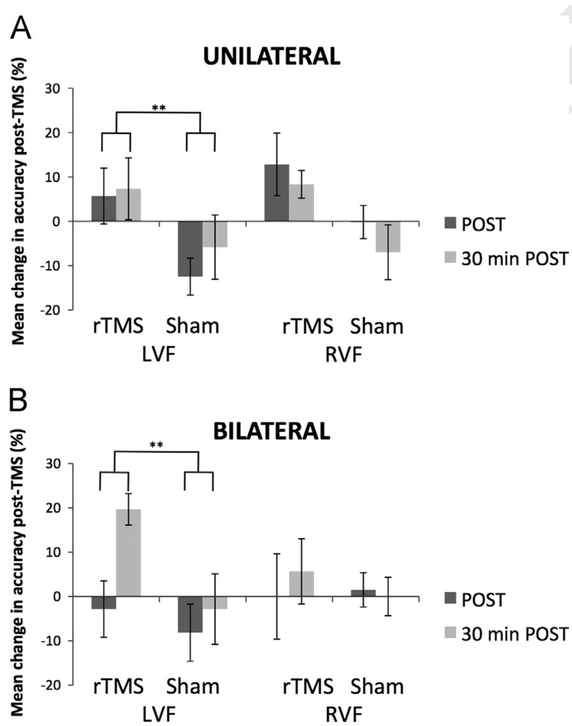

Fig. 4. Improvement after 1 Hz rTMS over the left parietal cortex relative to Sham. On the *Y*-axis the difference from baseline is shown, with positive values indicating improvement and negative values indicating impairment. The two graphs show results for the UNILATERAL (A) and BILATERAL (B) condition separately, immediately after stimulation (dark gray bars, POST) and 30 min after stimulation (light gray bars, 30 min POST).). A significant improvement after left parietal rTMS (relative to sham) was present in the left visual field only (LVF, leftmost bars in A and B) for both the unilateral and bilateral tracking conditions, reaching a peak at 30 min POST stimulation, where the strongest effect was seen in the bilateral condition (leftmost light gray bar, graph B). There was not a effect of stimulation for the right visual field (RVF). **Asterisks indicate significant difference.

All these studies suggest the use of rTMS as a tool for the rehabilitation of the behavioral deficits that are evident in the acute and sub-acute phase of a right-hemisphere stroke. However, TMS effects on patients' performances in the chronic phase are less studied, even if here we showed the majority of right parietal patients are still unable to achieve a full recovery. This is probably due to the “normal” performance that chronic patients show to neuropsychological assessment based on paper-and-pencil tasks (Bonato, 2012).

Here, and in our previous work (Battelli et al., 2001, 2003), we show that careful psychophysical analysis can reveal attentional deficits in the chronic phase of parietal stroke that are likely related to the patients ongoing behavioral difficulties (mainly based on self report or from family members). That is, when tested on threshold tasks that require a greater cognitive load (such as during bilateral visual tracking), patients can no longer compensate for their deficits. Indeed, the effect sizes we measured for the post-hoc *t*-test comparison between sham and active stimulations were large, indicating that the effect we found is not only statistically significant, but also meaningful (Cohen, 1988). Our sustained visual tracking attention task was designed precisely to measure a psychophysical threshold and, on the basis of this threshold, to detect changes in accuracy before and after stimulation. Importantly, for each patient we measured the speed threshold at which they performed at 75% accuracy both in the unilateral and bilateral conditions. This allowed us to bracket the patients' performance in the most sensitive regime, so as to better detect any changes in performance due to contralesional rTMS. Finally, counterbalancing active rTMS and sham-stimulation sessions controlled for possible learning effects across multiple sessions.

One might speculate about the potential mechanisms underlying our results. A recent paper using optogenetic in rats (Palmer et al., 2012) might help explain the neurophysiological basis and the basic mechanisms of inter-hemispheric inhibition and its pathological loss of balance after a unilateral stroke. In fact, it is well known that the corpus callosum consists almost entirely of excitatory fibers; however it is still unclear where interhemispheric inhibition happens. Palmer et al. (2012) found evidence suggesting that interhemispheric inhibition might result from the activation of local interneurons. In particular, they showed that callosal fibers exert inhibition indirectly via “layer 1” (inhibitory) interneurons, which in turn synapse to other neurons. This interhemispheric inhibition was evident only after bilateral hindpaw stimulation in the rat. This study provides neurobiological evidence of the hypothesized loss of interhemishperic inhibition (and consequent hemispheric imbalance) in lateralized impairment of attention in visual extinction. However this can only explain an acute effect, while in our experiment we found a more sustained effect that peaked at 30 min.

Indeed, one interesting aspect of the present results is the time course of the TMS effect. Visual inspection of Fig. 4 does not show improvement immediately after TMS but 30 min after active stimulation. Although at this point we can only speculate about the underlying physiological mechanisms, the delayed behavioral effect provides new evidence for the persistence of the TMS effects after stimulation that might indicate a longer-lasting mechanism like neuroplasticity (Siebner, Mentschel, Auer, & Conrad, 1999; Siebner, Rossmeier, Mentschel, Peineman, & Conrad, 2000). To the best of our knowledge, there are only two other studies that have found improvement after only one session of 1 Hz rTMS in right parietal patients (for a review see Müri et al. (2013)); however neither studies tested for a delayed effect after stimulation. Long lasting effects have been previously found, but with high frequency theta burst stimulation in acute patients only (Koch et al., 2012; Cazzoli et al., 2012); however fewer patients might be

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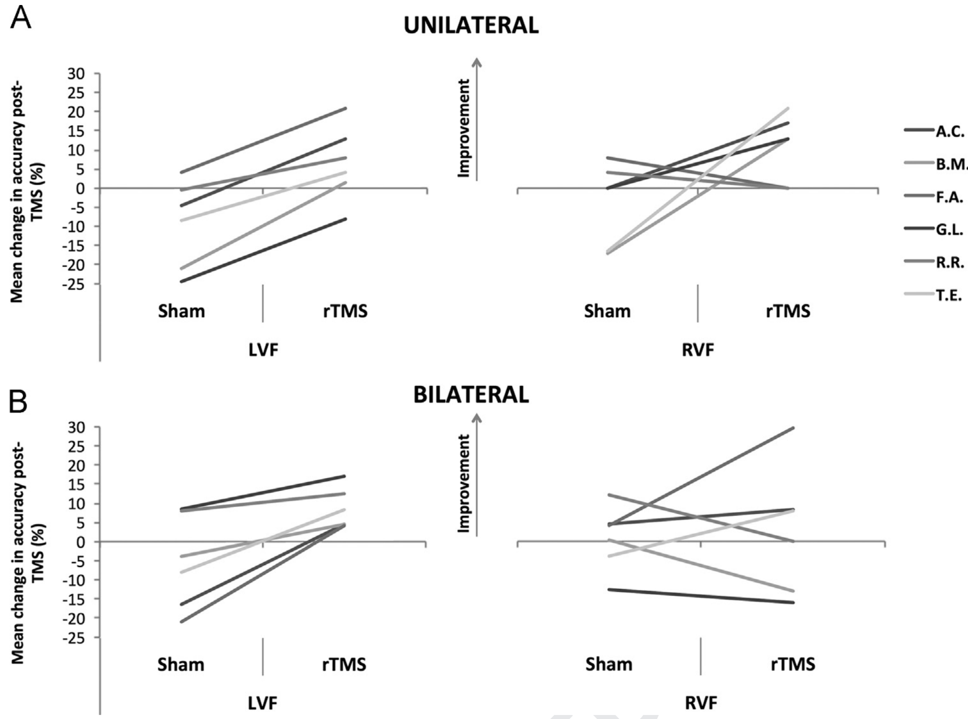

Fig. 5. Patients' individual data. On the *Y*-axis the difference from baseline is shown. The four graphs show results for the UNILATERAL (A) and BILATERAL (B) conditions separately. The graphs show a significant improvement after rTMS relative to Sham for the LVF (graphs on the left side for A and B) but not for the RVF (graphs on the right side for A and B). "POST" and "30 min POST" sessions are combined. The arrows between the graphs indicate that the values above 0 mean improvement after stimulation. Therefore positive values indicate an advantage relative to baseline, and negative values indicate a deficit relative to baseline.

eligible for these protocols due to the stimulation parameters required. Delayed effects ("offline consolidation") have also been observed in other experiments. For example, patients with Parkinson's disease treated with 5-Hz rTMS over M1, contralateral to the limb more affected by bradykinesia, showed a significant decrease in time to perform accurate pointing movements and the effect lasted between 20 min (Siebner et al., 1999) and 1 h (Siebner et al., 2000) after rTMS. In other cognitive domains, Schutter, van Honk, d'Alfonso, Postma and de Haan (2001) showed a significant reduction in anxiety and this reduction lasted following TMS (immediately, 35 and 65 min after stimulation) after 1 Hz TMS over the right prefrontal cortex. Interestingly, Kuo et al. (2013) have recently proposed a new high-definition transcranial direct current stimulation protocol using small electrodes to achieve a more focal stimulation (with a spatial resolution closer to what can be achieved with TMS). Similar to our study, this new stimulation protocol exerted a delayed effect that peaked 30 min after one stimulation session and lasted more than 2 h, consistent with longer lasting neuroplasticity after a more focal stimulation. However, to determine whether the delayed effect we found is consistent with neuroplasticity, we will need to use neuroimaging techniques to analyze the functional changes across time at the cortical sites involved in sustained attention (Plow et al., 2014).

The sustained improvement in attentional function with rTMS definitely is very intriguing. If the effects of low frequency rTMS substantially outlast the rTMS session itself, it raises the possibility that rTMS could provide more long-lasting therapeutic relief of deficits in right parietal patients. This result highlights the need for more systematic investigation of this effect, for instance, by running repeated stimulation sessions to see if an even longer-lasting effect can be achieved in the chronic patients and not only in the acute and sub-acute phases.

In conclusion, our results provide further and new evidence that low frequency rTMS might constitute a useful tool to promote recovery by directly intervening on the mechanisms that cause the loss of interhemispheric balance in parietal lobe patients.

Uncited references Q2

Cazzoli, Wutz, Müri, Hess and Nyffeler (2009); Vallar, Rusconi, Bignamini, Geminiani and Perani (1994)

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