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No causal effect of left hemisphere hyperactivity in the genesis of neglect-like behavior

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ABSTRACT

Spatial neglect is traditionally explained as an imbalance of the interhemispheric reciprocal inhibition exerted by the two hemispheres: after a right lesion, the contralesional hemisphere becomes disinhibited and its enhanced activity suppresses the activity in the lesioned one. Even though the hyperexcitability of the left hemisphere is the theoretical framework of several rehabilitation interventions using non-invasive brain stimulation protocols in neglect, no study has yet investigated directly the actual state of cortical excitability of the contralesional hemisphere immediately after the brain lesion. The present study represents the first attempt to directly assess the interhemispheric rivalry model adopting a novel approach based on the induction of neglect-like biases in healthy participants. Applying repetitive transcranial magnetic stimulation (rTMS) over the right posterior parietal cortex while concurrently recording the EEG activity allows to measure specific neurophysiological markers of cortical activity (i.e. TMS-evoked potentials, TEPs) both over the stimulated right hemisphere and over the contralateral homologous area. Besides the effectiveness of the protocol used in modulating behavior, our results show an inhibition of the cortical excitability of the directly stimulated parietal cortex (right hemisphere) and, most importantly, a comparable reduction of cortical excitability of the homologous contralateral (left) area. TEPs and additional electrophysiological measures reliably provide strong evidence for a bilateral hypo-activation following TMS induction of neglect-like biases. These results suggest that the parietal imbalance typically found in neglect patients could reflect a long-term maladaptive plastic reorganization that follows a brain lesion.

1. Introduction

Neglect patients fail to report, respond, or orient to stimuli presented on the opposite side of their brain lesion (Heilman and Valenstein, 1979) and they act as if the contralateral portion of space and their own body do not exist. Spatial neglect typically results as a consequence of a stroke, with lesion locations comprising the inferior parietal lobule, the superior temporal cortex and the ventrolateral frontal cortex as well as subcortical nuclei (Vallar and Perani, 1987; Karnath and Rorden, 2012). Neglect is more frequent, severe and persistent after right than left hemispheric damage (Stone et al., 1993), suggesting a right hemispheric dominance for spatial processing and attention (Heilman and Valenstein, 1979; Corbetta and Shulman, 2002). An important mechanism introduced by Kinsbourne (1977) to explain neglect is that of interhemispheric rivalry, that is the existence of reciprocally interactive opponent processes exerted by the two hemispheres. Following Kinsbourne's model, under normal conditions, the two hemispheres inhibit each other through the corpus callosum connections and attention can be deployed to the entire visual space, with each hemisphere attending to the contralateral space. After a lesion to the right hemisphere, the contralesional undamaged hemisphere is disinhibited and its enhanced activity further suppresses the activity in the lesioned one. Following this model, then, spatial neglect is caused not only by the inactivation of the right hemisphere but also by the hyperactivation of the intact, contralesional, hemisphere due to the release of inhibition from the damaged one. Corbetta and Shulman's (2002) model put together the two assumptions of right hemispheric dominance for attention and interhemispheric rivalry. Following this model, the presence and lateralization of neglect is

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explained as the result of both a lesion of the ventral attentional network (VAN, lateralized to the right hemisphere) and the interhemispheric imbalance of activity in the dorsal attentional system (DAN, present in both hemispheres) induced by the right brain lesion.

The role of hyper-excitability of the contralesional hemisphere in the genesis of spatial neglect has been the theoretical framework for several rehabilitative interventions of neglect using non-invasive stimulation protocols (Hesse et al., 2011; Oliveri, 2011; Müri et al., 2013). A widely used non-invasive brain stimulation technique is repetitive transcranial magnetic stimulation (rTMS), which interferes with the normal brain activity. TMS is suggested to induce "noise" in the cortex which interacts with the electrical activity and with the ongoing dynamics relevant to the task at hand (Miniussi et al., 2013; Silvanto and Muggleton, 2008). The effects, at behavioral level, of this noise induction also depend on the intensity and frequency of the stimulation. Relevant for the present study, it has been shown that low-frequency (≤ 1 Hz) rTMS has an inhibitory effect on the stimulated cortex (Maeda et al., 2000; Valero-Cabrè et al., 2006; Bourgeois et al., 2012). In the field of rehabilitation of spatial neglect, following the assumption of interhemispheric rivalry, rTMS has been applied to the contralesional cortex in chronic neglect patients in order to reduce its cortical hyperactivity. Although more systematic studies seem to be needed, these interventions proved to be successful in reducing neglect signs, thus reinforcing the idea that neglect is better explained as the imbalance of neural activity in the two hemispheres (Hesse et al., 2011; Oliveri, 2011; Müri et al., 2013).

Additional evidence in favor of the hyper-excitability of the left hemisphere (as indirectly assessed by parietal-M1 functional connectivity) in neglect patients come from TMS studies (see for review Koch et al. (2012)) investigating the cortical excitability of functionally interconnected areas. These studies investigated the cortical excitability of the left motor cortex in chronic neglect patients and healthy participants. The authors, using either twin-coil or tri-focal TMS methods, consistently demonstrated that the excitability of the contralesional hemisphere, as measured by the amplitude of motor evoked potentials, was enhanced.

Despite these accumulating pieces of evidence, we believe that the most direct way to test whether interhemispheric rivalry is the cause of neglect would be to directly investigate, with brain imaging techniques, the activation of the left hemisphere immediately after a brain lesion in patients or during a TMS-induced hypo-activation of the right hemisphere in healthy subjects. Data from neuropsychological literature are somehow controversial. On the one hand, studies finding hyperactivation of the left hemisphere investigated patients with subacute/chronic neglect, thus being unable to exclude the possibility of plastic rearrangement of the function. On the other hand, studies investigating patients with acute neglect (first hours/days after stroke) cannot confirm the existence of a hyperactivation of the left hemisphere (Fiorelli et al., 1991; Perani et al., 1993; Vallar et al., 1988; Umarova et al., 2011). With respect to the studies with healthy participants, to our knowledge, only one paper directly investigated the effects of TMS on the activity of the contralateral hemisphere using a task typically adopted to diagnose visuo-spatial neglect (Ricci et al., 2012). In a clever and technically demanding experiment, Ricci and collaborators used the interleaved TMS/fMRI technique while the participants were requested to perform a line bisection judgment task (i.e. the landmark task), a task largely used with neglect patients (Milner et al., 1993; Bisiach et al., 1998). TMS was applied to the right inferior parietal lobule (IPL), a neural site consistently found to be effective in inducing neglect-like signs in healthy participants (Sack, 2010). As expected, the authors found that TMS of IPL suppressed the activity of the underlying cortex. Importantly, TMS had also the effect of inducing hypo-activation of the contralateral homologous IPL, thus being at odd with the assumption of interhemispheric rivalry. The authors interpreted their results in terms of diaschisis and they hypothesized that hemispheric imbalance found in neglect patients could be due to a maladaptive plasticity that emerges over time (see also Section 4).

The main thrust of the present paper is to directly test the interhemispheric rivalry models by inducing neglect-like behavior in healthy participants through the application of low-frequency TMS over the right hemisphere and by concurrently recording the electroencephalographic (EEG) activity. The combination of TMS and EEG allows the measurement of physiological markers of cortical activity (i.e., TMS-evoked cortical potentials, TEPs) in both hemispheres during the TMS induction of neglect-like biases. TEPs represent a clear and direct measure of cortical excitability and can be used to assess the state of cortical activity also in the so-called silent-areas that do not produce a peripheral marker of central excitability, like the parietal cortex (Ilmoniemi et al., 1997; Komssi et al., 2002, 2004; Kahkonen et al., 2005; Bonato et al., 2006; Miniussi and Thut, 2010; Pellicciari et al., 2013). Importantly, the properties of TEPs seem ideal for the purposes of the present paper. Indeed, here, we adopted an off-line interactive approach (Miniussi and Thut, 2010) by using EEG–TMS co-registration while the participant performed a task before and after rTMS. Thanks to this approach it is possible to investigate not only the effects of the train of stimulation in the stimulated area but, more importantly, to gather information on the induced electrical changes in distant but functionally connected areas (i.e. effective connectivity. Miniussi et al., 2013; Bortoletto et al., 2015) and on their excitatory/inhibitory relationship. More specifically, given the properties of the spreading of activity induced by TMS (Ilmoniemi et al., 1997; Miniussi et al., 2013; Bortoletto et al., 2015), if the inhibition of an area X (i.e. the target area of rTMS) is followed by a reduced activity in an area Y it can be assumed that the two areas are positively connected (excitatory connection), conversely if the inhibition of an area X (i.e. the target area of rTMS) is followed by an enhancement of the activity in an area Y it can be assumed that the two areas are negatively connected (inhibitory connection).

The logic of the present study is the following. Low-frequency rTMS of the right hemisphere should have a twofold effect, both at a behavioral and a neural level. Firstly, at behavioral level, participants should present with neglect-like behavior. Specifically, after the application of rTMS, rightward bisection errors are expected in a line bisection task, a task widely used to detect neglect in neurological patients. Secondly, at neural level, rTMS is expected to down-regulate the underlying cortical activity (e.g. Fierro et al., 2000; Brighina et al., 2002) and TEPs with a reduced amplitude are expected over the right hemisphere at the end of the stimulation session. Importantly, the direct test of interhemispheric rivalry relies on the investigation of the effects induced by rTMS on the cortical activity contralateral to the site of stimulation. If the interhemispheric rivalry assumption is tenable, TEPs with an enhanced amplitude are expected over the left hemisphere, as a consequence of the release from inhibition caused by the application of rTMS to the right hemisphere.

In the present paper we also evaluated behavior (reaction times to visual stimuli) and cortical excitability (event-related potentials-ERPs to visual stimuli) before and after rTMS application, in order to have additional measures of cortical activity. Specifically, visual stimuli presented contralateral to the stimulated cortex are expected to be reacted to slower and to evoke smaller ERP components after TMS. To support interhemispheric rivalry, two strict predictions have to be respected. At the behavioral level, reaction times to visual stimuli presented ipsilateral to the site of rTMS need to be faster, again as a consequence of the release from inhibition induced by rTMS over the right hemisphere. Likewise, at the neural level ERP components to visual stimuli presented

ipsilateral to the site of rTMS need to be enhanced.

2. Method

2.1. Participants

Twenty right-handed (as assessed with the Edinburgh Handedness Inventory; Oldfield, 1971) healthy volunteers (13 females), aged 19–34 years (mean 25.47 years, sd 4.07 years), took part in the experiment. They all had normal or corrected-to-normal visual acuity and no history of neurological or psychiatric disorders. All gave their written informed consent to participate in the experiment. The experiment was carried out according to the principles laid down in the 1964 Declaration of Helsinki and approved by the local Ethics Committee. The data from six participants were not included in the analysis because of high noise in the EEG recordings. Therefore, the research sample consisted of 14 participants (9 females; mean age 24.64 years, sd 3.67 years).

As assessed by a safety screening questionnaire (adapted from Rossi et al. (2011)), the participants were negative for all the risk factors associated with TMS: none reported neurological disorders, cardiac pacemaker, any history of epilepsy or migraine, current treatment with any psychoactive medication or pregnancy.

2.2. Experimental design

Fig. 1 illustrates the experimental design. After applying the cap with electrodes for EEG recording, we measured the motor threshold in order to set the stimulation parameters (see TMS protocol session). The 14 participants took part in two experimental sessions (rTMS/Sham) and a subset of them took part in an additional control session ("Rest"), see below. The two main experimental sessions (rTMS/Sham) were performed in consecutive days. The sequence of the tasks for each of the two experimental sessions was as the following. Prior to the stimulation protocols, the participants had to perform the line bisection task (about 2 min duration) followed by the detection task (12.5 min duration). After the stimulation protocols, the participants were asked to perform two line bisection tasks, one before and one after the post-stimulation detection task. The main stimulation protocols, which lasted for 30 min, were constituted by the rTMS and the Sham stimulation protocols, conducted in two separate days and counterbalanced among participants. An additional control session ("Rest") was performed on a subset of 7 participants taking part in the main experiment, in order to test the effects of perceptual learning on RTs and EEG activity due to the repetition of the task. During this session, the participants performed the detection task before and after a rest period of 30 min in which they were requested to do nothing and no stimulation was administered (Fig. 1). This session was performed at least a month after the main experiment. In order to reduce uncontrolled effects of "mind wandering" or non-specific brain activity related to thoughts or mental imagery, which could affect the ongoing activity in the targeted systems and associated networks (Silvanto and Muggleton, 2008), the participants were instructed to relax and free their mind during stimulation. The experimenter checked with the participants if they were following this instruction every 10 min. This procedure was adopted in both the stimulation protocols (TMS, Sham) and in the control ("Rest") session, to render all the protocols homogeneous with respect to the instructions.

2.3. Line bisection task

Participants were required to bisect a series of five 20 cm long and 1.5 mm thick black horizontal lines presented on five separate landscape A4 sheets of white paper aligned to the sagittal midline of the participant's trunk. Errors were measured with approximation to the nearest mm. Positive values indicate a rightward error and negative values a leftward error. This task (Fig. 1) was administered three times: before the rTMS/Sham stimulation protocol (hereafter named as "LB-baseline" condition), immediately after the stimulation (hereafter named as "LB-post 1" condition) and at the end of the experiment (hereafter named as "LB-post 2" condition).

2.4. Simple detection task

The participants were seated in front of a 17″ IBM-G96 CRT monitor (background luminance 0.01 cd/m^2) with the eyes at 57 cm from its center. A chin rest helped stabilizing the head of the participants. At the beginning of the trial, a 1000 Hz tone of 200 ms duration signaled the participants to fixate a small cross in the center of the screen and to wait for the appearance of a visual stimulus. The interval between the tone and the stimulus onset varied randomly within a temporal window of 200–600 ms. The stimulus was a single lateralized checkerboard (mean luminance=3.67 cd/m^2, spatial frequency=2 cycles/degree of visual angle, Michelson contrast=1) with an exposure duration of 85 ms, subtending 2.5° of visual angle and presented at 5° from the fixation cross along the horizontal meridian, either to the right or to the left visual field. Participants were asked to respond as quickly as possible to the appearance of a checkerboard by pressing the spacebar of a PC keyboard with the right or the left index finger in four different blocks according to an ABAB sequence (half of the participants started with the left hand and the other half with the right hand). There were 140 trials for each visual hemifield (plus 40 catch trials in which no visual stimulus

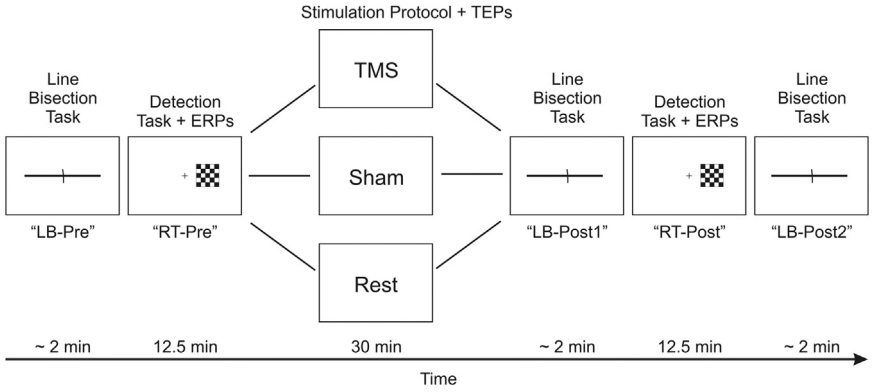

Fig. 1. Task sequence. The figure depicts the time sequence of the two main sessions (rTMS and Sham) and the supplementary control session (Rest).

was presented following the tone and no response was required) for a total of 320 trials for the entire experiment. In order to maintain the duration of the entire detection task fixed (in mean of 12.5 min), the duration of each of the three pauses among the blocks of trials was set at 25 s. After 15 s in which the word "pause" was presented above the fixation cross, a countdown from 9 to 0 started running (1 s duration for each displayed number), signaling the participant of the beginning of the subsequent block of trials.

The participants were instructed to suppress saccades toward the site of stimulus presentation and to avoid blinking in order to minimize EEG artifacts. Reaction times (RTs) faster than 140 ms or slower than 650 ms were considered as anticipations and late responses, respectively, and were not included in the statistical analyses. The overall mean of discarded trials was 2.02 (0.72%).

The stimuli were generated and manual responses were recorded using E-Prime 1.1 (SP3) software (Psychology Software Tools, Pittsburgh, PA). The detection task (Fig. 1) was administered twice: before (hereafter named as "DT-Pre" condition) and after (hereafter named as "DT-Post" condition) the rTMS/Sham stimulation protocols and the control session ("Rest").

2.5. TMS protocol

rTMS was delivered through a 70 mm figure-of-eight Magstim Air Film Coil connected with a Magstim Rapid^2 system (maximum output 3.5 T) (Magstim Company Limited, Whitland, UK). The stimulation was delivered at low frequency (1 Hz) for 30 min (total number of pulses = 1800) at 90% (mean 55.22% of Maximum Stimulator Output, MSO) of motor threshold (mean 61.36% of the MSO), i.e. stimulus parameters known to reduce cortical excitability for several minutes beyond the duration of the TMS trains (Maeda et al., 2000; Valero-Cabrè et al., 2006). Motor threshold was measured as the minimum stimulation intensity able to elicit a motor evoked potential (MEP) of $\geq 50\ \mu V$ in the left first dorsal interosseous muscle in five of ten consecutive stimulations (Rossini et al., 1994). rTMS was applied unilaterally over the right parietal cortex between P4 and P8 electrodes of the 10–20 International EEG system (i.e. at the position of the P6 electrode), corresponding to the right inferior parietal lobe (e.g. Brighina et al., 2002; Fierro et al., 2000). This site was selected because (1) this area is the most frequently damaged in patients with spatial neglect and (2) it has proved that, if properly stimulated with TMS, can induce neglect-like phenomena in healthy participants (e.g. Brighina et al., 2002; Fierro et al., 2000). The TMS coil was placed tangentially on the target scalp site with the handle pointing backwards, so as to induce a posterior-to-anterior current direction in the underlying cortical surface. In order to stabilize the coil in the correct position and orientation with respect to the scalp, the coil was fixed in the targeted position by means of a mechanical arm (Magstim Articulated Coil Stand) and the participants wore a custom-made collar for the entire duration of the stimulation protocol preventing any head movements. Moreover, the position of the coil was constantly checked by the experimenter and, in the rare occasions it was needed, corrected. The stimulation protocol (stimulus intensity, frequency and duration of the pulse train) was selected according to the international safety guidelines (Rossi et al., 2009) and commercial earplugs were used to protect the participants from the noise associated with TMS (Rossi et al., 2009). None of the participants reported negative effects during or after stimulation. For the Sham condition we used the same parameters as for the rTMS session. In this session, however, in order to reduce the intensity of the magnetic field reaching the scalp (Stokes et al., 2005), a custom-made 3-cm-thick block of polystyrene was placed between the coil and the scalp. The formula proposed by Stokes et al. (2005) states that for every millimeter from the stimulating coil, an additional 3% of TMS output would be required to induce an equivalent output. Given the interposition of the polystyrene block, to be effective the intensity of the Sham stimulation should have been set at 151% of the MSO. However, the same parameters were set for both the TMS and Sham protocols (55.22% MSO), thus ensuring that the Sham stimulation was ineffective.

2.6. EEG recording

TMS-compatible EEG equipment (BrainAmp, Brain Products GmbH, Munich, Germany) was used to record EEG signals (BrainVision Recorder). The EEG activity was continuously recorded from a Fast'n Easy cap with 27 TMS-compatible Ag/AgCl pellet pin electrodes (EasyCap GmbH, Herrsching, Germany) placed according to the 10–20 International System (O1, O2, P7, P3, Pz, P4, P8, CP5, CP1, CP2, CP6, T7, C3, Cz, C4, T8, FC5, FC1, FC2, FC6, F7, F3, Fz, F4, F8, Fp1, Fp2). Additional electrodes were used as reference and ground and for the electro-oculogram. The ground electrode was placed in AFz, i.e. at the maximal distance from the stimulating TMS coil. All scalp channels were online referenced to the right mastoid (RM) and then re-referenced offline to the left mastoid (LM). Horizontal and vertical eye movements were detected respectively with electrodes placed at the left and right canthi and above and below the right eye. The impedance of all the electrodes was kept below 5 kΩ. The EEG was recorded at 5000 Hz sampling rate with a time constant of 10 s as low cut-off and a high cut-off of 1000 Hz. The EEG signal was processed off-line using Brain Vision Analyzer 1.04.

2.7. TMS-evoked potentials (TEPs) analysis

TEPs were acquired during the 30 min of rTMS protocol. Ideally, a specific session of TEP acquisition would have to precede and follow the rTMS protocol, in order to have a clear measure of cortical excitability before and after the inhibitory intervention. However, this additional session would have extended the length of an already demanding experiment and, most importantly, could have affected the effects of the subsequent rTMS protocol. Therefore, we found reasonable to investigate TEPs induced by the inhibitory protocol itself, assuming to observe a difference between the amplitude of the first and the last pulses of the protocol, if the rTMS protocol had been effective in inducing an inhibitory effect. The epoching of TMS-related EEG was performed off-line, dividing the continuous EEG signal into epochs from 100 ms before the TMS pulse (baseline) to 300 ms after. Epochs were then baseline corrected and visually inspected in order to remove all trials contaminated by eye movements and blinking artifacts, involuntary motor acts or excessively noisy EEG. TEPs were obtained by averaging epochs for each participant, separately for the first (early rTMS) and the last (late rTMS) 180 pulses of the stimulation session (corresponding to the first and last 10% of the total number of trials), in order to get a direct index of the expected cortical excitability reduction.

Given that TMS artifact influences the recording of meaningful EEG data in a period of few milliseconds after the delivery of the magnetic field (Veniero et al., 2009), a "linear interpolation" function was applied. This function cuts out one time interval of the segmented data and replaces it with a linearly interpolated artificial interval. The "linear interpolation" function was applied in the time range comprised between 1 ms before to 15 ms after the TMS pulse. Due to the presence of a strong TMS artifact, only the data from 10 out of 14 participants were included in this analysis. The analyses were conducted considering P8, which was the electrode closest to the stimulation site, and the contralateral electrode P7. In order to test the spatial specificity of the effects

induced by the rTMS protocol, we included in the analysis an additional electrode (Cz) to be considered as a control site. Statistical analyses were performed on the mean amplitude values acquired in the time window between 60 ms and 85 ms after the delivery of the TMS pulse. This time window was set after an exploratory analysis of the data across the entire epoch, using successive *T*-test comparisons (Murray et al., 2002; Guthrie and Buchwald, 1991), which showed no earlier effects of the experimental variables. During 30 min of Sham sessions we acquired EEG activity locked to the placebo TMS pulse, in order to monitor the unspecific effects (e.g., flow of time; acoustic sensations) that could account for modulations of cortical excitability, but are not directly due to the magnetic stimulation.

2.8. Event-related potentials (ERPs) analysis

We studied visual ERPs elicited by the checkerboard presentation during the simple detection task. Continuous data were filtered off-line with a 40 Hz high cut-off filter. Epochs were created starting from 200 ms before and ending 600 ms after stimulus onset and baseline corrected from −200 ms to 0 ms. All epochs were visually inspected in order to discard epochs with eye movements artifacts (blinks or saccades), epochs with EEG exceeding ±100 μV and other noise sources. For every stimulation protocol (rTMS, Sham, Rest), epochs were averaged separately for time (DT-Pre, DT-Post) and for the visual hemifield (right, left) where stimuli were presented during the detection task. The amplitude of the P200 peak, typically maximal over posterior sites, was registered from P4 and P3 electrodes, where it reached the largest amplitude values. The amplitude of P200 component was calculated as the peak with the highest amplitude within a 200–260 ms post-stimulus time window.

3. Results

3.1. Line bisection task

Mean deviations (in mm) ± standard error of the mean (SEM) from the geometrical midpoint of the lines as a function of the type of stimulation protocol (rTMS, Sham) and time of testing (LB-Pre, LB-Post) are shown in Fig. 2. A 2 × 3 repeated measure ANOVA on the mean deviation scores with Stimulation Protocol (rTMS, Sham) and Time (LB-baseline, LB-post 1 and LB-post 2) as within-subjects factors was carried out. Results showed a significant main effect of Time [$F(2,26)=8.24$, $p \leq 0.01$, $\eta_p^2=0.39$] and a significant Stimulation Protocol by Time interaction [$F(2,26)=9.25$, $p \leq 0.01$, $\eta_p^2=0.42$]. No significant effect was found for Stimulation Protocol [$F(1,13)=1.56$, $p=0.23$, $\eta_p^2=0.11$]. A series of post-hoc Bonferroni-corrected *T*-tests revealed a reliable rightward deviation between baseline condition (LB-baseline, mean: 0.06 mm, SEM: 0.85 mm) and both the first [LB-post 1, mean: 2.96 mm, SEM: 1.01 mm; $t(13)=-3.45$, $p \leq 0.01$, $\eta_p^2=0.48$] and the second post-stimulation condition [LB-post 2, mean: 1.94 mm, SEM: 0.82 mm; $t(13)=-2.93$, $p \leq 0.05$, $\eta_p^2=0.40$] only in the rTMS protocol. No such effects were present in the Sham stimulation protocol (all $p > 0.05$). These results indicate that low frequency rTMS over the right inferior parietal cortex was effective in inducing a neglect-like behavior (i.e. a rightward deviation in a line bisection task) in healthy participants while this was not the case using a Sham protocol.

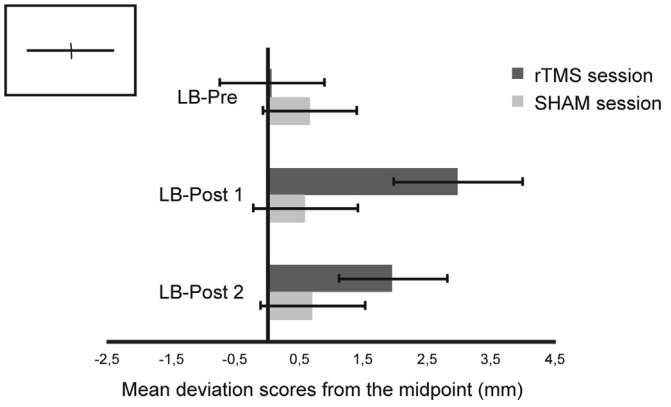

Fig. 2. Line bisection. Mean deviation scores (in mm) from the geometrical midpoint of the line for the two stimulation sessions (rTMS, Sham) as a function of time: before stimulation (LB-Pre), immediately after (LB-Post 1) and at the end of the experiment (LB-Post 2). Whiskers represent the standard error of the mean.

3.2. TMS-evoked potentials (TEPs)

TEPs elicited in the first 180 pulses (early rTMS) and in the last 180 pulses (late rTMS) of the rTMS protocol are depicted in Fig. 3 (upper panel). A 2-way repeated measure ANOVA on TEPs mean amplitudes elicited by rTMS protocol with Time (early rTMS, late rTMS) and Site (P8, P7, Cz) as within-subjects factors was carried out. No significant main effect was found for Time [$F(1,9)=1.90$, $p=0.20$, $\eta_p^2=0.18$] and Site [$F(2,18)=2.02$, $p=0.16$, $\eta_p^2=0.18$] factors. Importantly, the analysis showed that the Site reliably interacted with Time [$F(2,18)=11.36$, $p < 0.01$, $\eta_p^2=0.56$]. A series of post-hoc *T*-test showed that, with respect to prior stimulation (P8 electrode: mean: 3.39 μV, SEM: 0.70 μV; P7 electrode: mean: 2.96 μV, SEM: 0.56 μV), cortical excitability was reliably reduced as a consequence of rTMS, both on the right parietal cortex (mean: 1.94 μV, SEM: 0.49 μV), i.e. beneath the stimulation site [P8 electrode: $t(9)=2.81$, $p \leq 0.05$, $\eta_p^2=0.47$], and on the left hemisphere (mean: 1.68 μV, SEM: 0.37 μV), i.e. the homologous contralateral cortex [P7 electrode: $t(9)=2.72$, $p \leq 0.05$, $\eta_p^2=0.36$]. No such effect was found considering the electrode Cz [$t(9)=-1.37$, $p=0.20$, $\eta_p^2=0.17$], thus supporting the specificity of the effect induced by rTMS over ipsilateral and contralateral parietal cortices.

The same statistical analysis was applied to the EEG activity locked to the sham TMS pulse measured in the same time window considered for TEP analysis (i.e. from 60 to 85 ms post-TMS pulse), (see Fig. 3, lower panel), with Time (early Sham, late Sham) and Site (P8, P7, Cz) as within-subjects factors. No significant main effect was found for Time [$F(1,9)=0.86$, $p=0.38$, $\eta_p^2=0.09$] and Site [$F(2,18)=4.05$, $p=0.06$, $\eta_p^2=0.31$] factors. Furthermore, the interaction between Time and Site was found not to be significant [$F(2,18)=1.78$, $p=0.21$, $\eta_p^2=0.17$], testifying that the reduction of cortical excitability observed after rTMS was not due to unspecific effects.

Taken together, the present results showed that 30 min of low frequency rTMS induced a reduction of the cortical excitability of both the stimulated right parietal cortex and the left contralateral homologous areas.

3.3. Detection task

Mean reaction times as a function of side of presentation, type of stimulation protocol and time of testing are shown in Fig. 4. A 3-way repeated measures ANOVA on RTs with Stimulation Protocol (rTMS, Sham), Time (DT-Pre, DT-Post) and Hemifield (left, right) as within-subjects factors was carried out. The only effect found to be significant was the Stimulation Protocol by Time interaction [$F(1,13)=6.16$, $p \leq 0.05$, $\eta_p^2=0.32$]. Post-hoc Bonferroni-corrected *T*-tests on the mean RTs collapsed for the side of presentation (an effect not found to be significant) revealed that RTs (mean: 287 ms, SEM: 6.02 ms) after the Sham stimulation were faster [$t(13)=2.16$, $p \leq 0.05$, $\eta_p^2=0.26$] than those before Sham

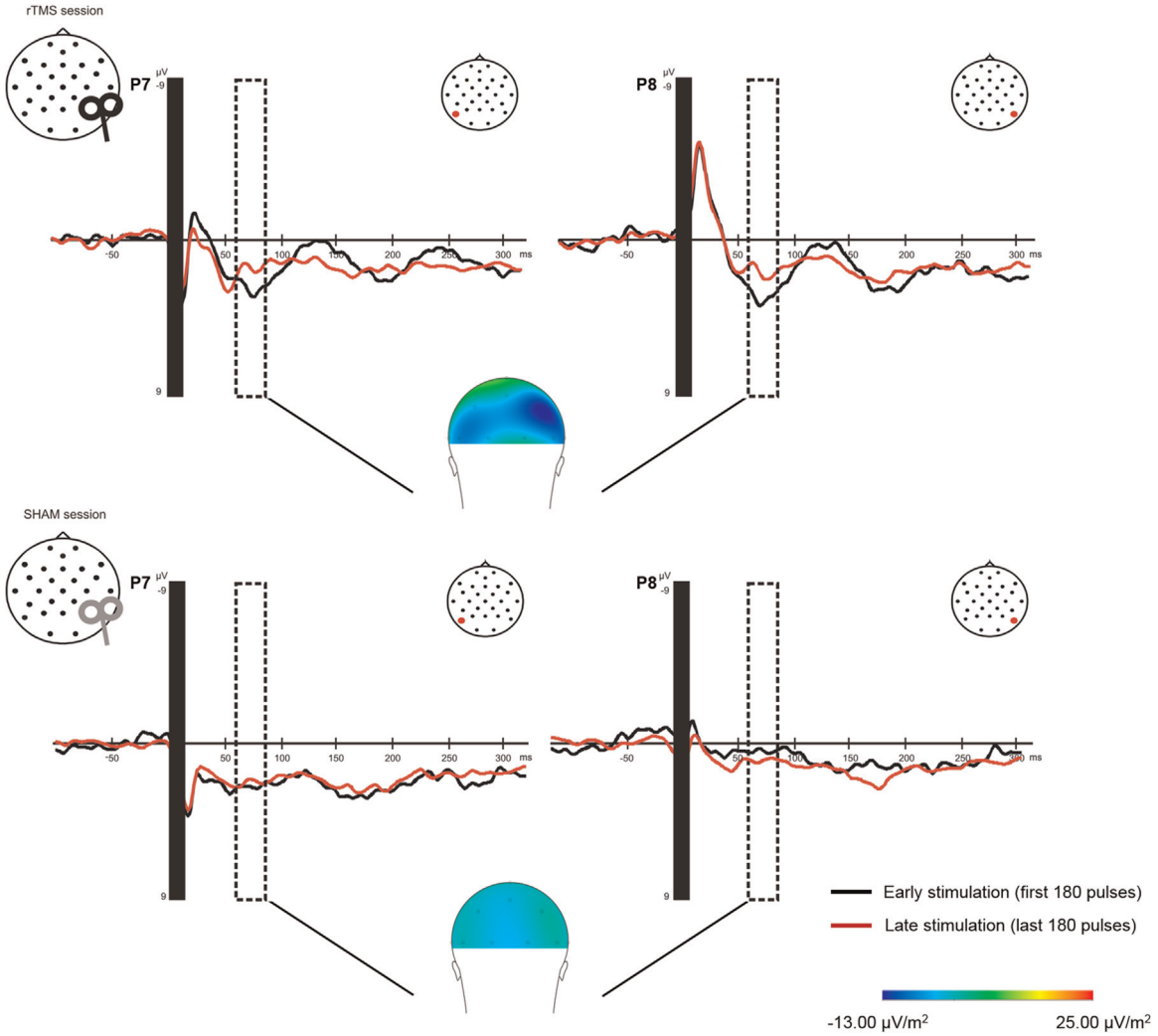

Fig. 3. TMS-evoked potentials. TEPs elicited by the first 180 pulses (early stimulation, in black) and by the last 180 pulses (late stimulation, in red) for the rTMS (up) and Sham (down) stimulation protocols recorded ipsilaterally (right) or contralaterally (left) to the stimulation site. The black boxes indicate the time window in which the "linear interpolation" was applied. Black dotted boxes superimposed on the waveforms mark the time window ranging from 60 to 85 ms in which analysis were computed. Topographical maps (back view) represent the difference between late and early stimulation in the time window between 60 and 85 ms after rTMS pulse. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

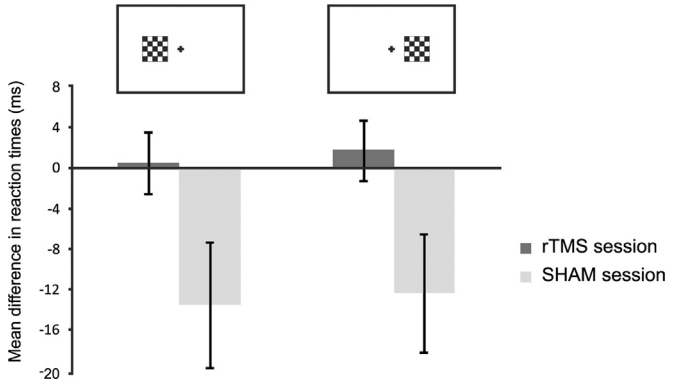

Fig. 4. Reaction times. Mean difference (DT-after minus DT-before) in reaction times for the two stimulation sessions as a function of the stimulus location. Whiskers represent the standard error of the mean.

stimulation (mean: 299.92 ms, SEM: 8.13 ms). No such effect was found for the rTMS protocol for which RTs before (mean: 293.59 ms, SEM: 6.46 ms) and after (mean: 294.71 ms, SEM: 7.58 ms) rTMS remained unchanged [$t(13)=-0.38$, $p=0.71$, $\eta_p^2=0.01$]. Importantly, different from what one would expect on the basis of "inter-hemispheric rivalry" models, RTs were not modulated by the side of presentation (no significant effect [$F(1,13)=0.00$, $p=0.99$, $\eta_p^2=0.00$] of Stimulation Protocol by Time by Hemifield interaction). Indeed, "inter-hemispheric rivalry models" would predict that after rTMS the responses to left-sided stimuli would be slower and the responses to right-sided stimuli would be faster. On the contrary, no effect of side of presentation was found. It could, however, be surmised that the detection task we used did not have enough sensitivity to detect a change in RTs due to rTMS, either because it is a simple detection task or because photopic stimuli were used. Contrary to this idea, such an effect on RTs was found for the Sham session.

In order to ascertain that the effects found with Sham stimulation could be due to perceptual learning (Ding et al., 2003; Song et al., 2007) or to a more general stimulus-response learning due to adaptation/habituation (Qu et al., 2010), the same paradigm was performed in the Rest condition and the same analysis on RTs was performed. In line with this interpretation, the results showed a shortening of RTs [$F(1,6)=9.83$, $p\leq 0.05$, $\eta_p^2=0.62$] after a period of 30 min of rest (before: mean: 317.31 ms, SEM: 11.38 ms; after: mean: 301.86 ms, SEM: 7.66 ms) whereas no effect of the side of stimulus presentation was found [$F(1,6)=0.86$, $p=0.39$, $\eta_p^2=0.13$].

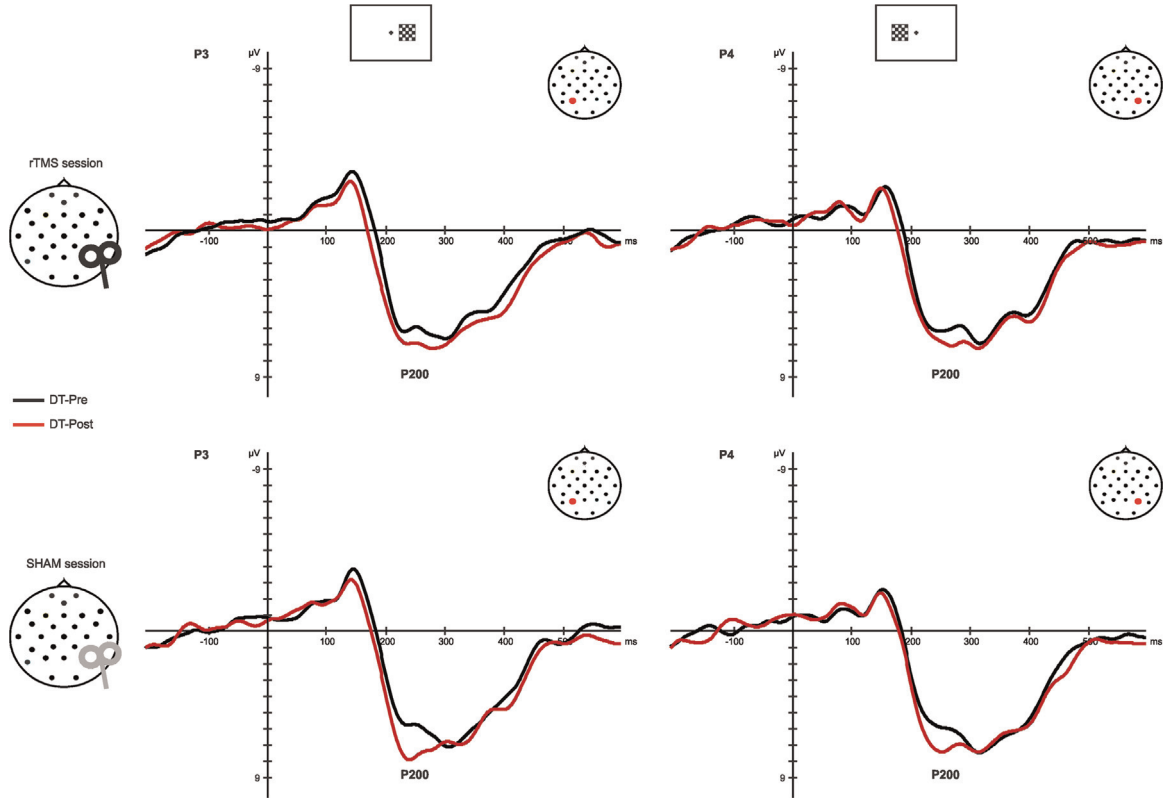

Fig. 5. Event-related potentials. ERPs for the rTMS (up) and Sham (down) stimulation protocols recorded ipsilaterally (right) or contralaterally (left) to the stimulation site as a function of time: before stimulation (DT-Pre, in black) and immediately after (DT-Post, in red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Event-related potentials (ERPs)

Fig. 5 shows the ERPs elicited by the visual stimulus presented contralaterally to P3 and P4 electrodes as a function of time of testing and type of stimulation protocol. A 3-way repeated measures ANOVA on the amplitude of the P200 component with Stimulation Protocol (rTMS, Sham), Time (DT-Pre, DT-Post) and Hemifield (left, right) as within-subjects factors was carried out.

Results showed a significant main effect of Time [$F(1,13)=13.99$, $p\leq 0.01$, $\eta_p{}^2=0.52$] and of the interaction between Stimulation Protocol and Time [$F(1,13)=7.56$, $p\leq 0.05$, $\eta_p{}^2=0.37$]. In order to better substantiate this interaction, the data of the hemifield of presentation were collapsed and a series of post-hoc Bonferroni corrected *T*-tests on the amplitude of P200 component was then performed. This analysis revealed that after 30 min of Sham stimulation, the amplitude of the P200 component (DT-Post: mean: 8.02 μV, SEM: 1.04 μV) was higher [$t(13)=-4.47$, $p\leq 0.001$, $\eta_p{}^2=0.61$] than that observed in the pre-stimulation task (DT-Pre: mean: 6.31 μV, SEM: 0.87 μV). Importantly, this effect was not observed when the second detection task was performed after the low frequency rTMS: for this protocol, indeed, the amplitude of the P200 component prior (DT-Pre: mean: 6.52 μV, SEM: 0.98 μV) was similar [$t(13)=-1.64$, $p=0.12$, $\eta_p{}^2=0.17$] to that observed after (DT-Post: mean: 7.10 μV, SEM: 1.09 μV) rTMS stimulation. No significant effect of the Stimulation Protocol by Time by Hemifield interaction [$F(1,13)=0.42$, $p=0.53$, $\eta_p{}^2=0.03$] was found, revealing that the modulation of the amplitude of the P200 component occurred regardless of the side of presentation of visual stimuli. This additional piece of evidence, in line with what observed with the RT task, argues against the "inter-hemispheric rivalry model" predictions.

In addition, the same analysis performed on the RTs for the Rest condition was used for the ERPs data in order to establish that the effects found with Sham stimulation were due to perceptual learning (Ding et al., 2003; Song et al., 2007). A 2-way repeated measure ANOVA on the amplitude of the P200 component with Time (DT-Pre, DT-Post) and Hemifield (left, right) as within-subjects factors was carried out. The only effect found to be significant was the Time factor [$F(1,6)=11.20$, $p\leq 0.05$, $\eta_p{}^2=0.65$]. Post-hoc Bonferroni-corrected *T*-tests (regardless the Hemifield factor, an effect not found to be significant) revealed that after (DT-Post: mean: 6.72 μV, SEM: 0.84 μV) 30 min of rest the amplitude of the parietal P200 component reliably increased [$t(6)=-3.35$, $p\leq 0.05$, $\eta_p{}^2=0.46$] with respect to that observed before (DT-Pre: mean: 5.34 μV, SEM: 0.93 μV). No effect of side of presentation was found (all $p>0.05$), suggesting that the enhancement of the P200 amplitude occurred equally in both hemispheres.

4. Discussion

In the present experiment, we tested whether the inter-hemispheric rivalry models (Kinsbourne, 1977; Corbetta and Shulman, 2002) can explain neglect-like behavior in healthy participants. To do so, 14 healthy participants were asked to perform a simple detection task of lateralized checkerboards before and after a low-frequency rTMS of the right inferior parietal cortex able to induce a reduction of cortical excitability. Moreover, EEG signals recorded during the whole experiment were used as the index of the cortical changes in excitability induced by rTMS. By means of a line bisection task performed prior and after rTMS we ascertained that the protocol used was effective in inducing neglect-like behavior in healthy participants, in that the participants showed significant rightward deviation errors after stimulation. Moreover, the cortical excitability of the stimulated area and of distant but interconnected areas, was found to be reduced at the end of the rTMS

protocol, as measured by TEPs. This result is a further confirmation of the efficacy of our stimulation protocol in inhibiting cortical activity. Interestingly for the present discussion, TEPs showed that low frequency rTMS induced a comparable reduction of the cortical excitability of both the stimulated (right) and the contralateral (left) parietal cortex. The specificity of this result (i.e., no effect on the control site Cz and no effect in the analysis applied to the EEG activity locked to the sham TMS pulses) allows to exclude that this reduction of cortical excitability may be ascribed to unspecific effects, strengthening its relation to the neglect-like bias induced during the rTMS protocol. Since TEPs amplitude is an unequivocal measure of cortical reactivity (Ilmoniemi et al., 1997; Komssi et al., 2002, 2004; Kahkonen et al., 2005; Bonato et al., 2006; Miniussi and Thut, 2010; Pellicciari et al., 2013), bilateral reduced TEP amplitudes after rTMS can be directly explained as a reduction of cortical excitability in both hemispheres, thus providing strong evidence for bilateral cortical hypo-activation induced by rTMS of the right hemisphere (i.e. excitatory connections between the two parietal cortices). This first piece of evidence is in direct contrast to the predictions of the inter-hemispheric rivalry models. According to these models, indeed, the reduced excitability of the right parietal areas (induced by TMS or a lesion to that area) should produce an increased cortical excitability in the left parietal cortex as a consequence of the release of the reciprocal inhibition of the two hemispheres (i.e. inhibitory connections between the two parietal cortices).

Additional evidence comes from behavioral and EEG data obtained during the detection tasks performed prior and after rTMS. Firstly, the response speed to the visual stimuli was found unchanged after rTMS while it was fastened after an ineffective stimulation (Sham) protocol, thus indicating an inhibitory effect of rTMS on a learning process induced by task repetition (see also the results obtained in the "Rest" session). Importantly, the inhibitory effect of rTMS was generalized to both the right and the left visual stimuli. This result is at odds with the predictions of the inter-hemispheric rivalry models. These models, indeed, predict that after inhibitory rTMS (or a brain lesion) to the right hemisphere, left-sided stimuli are responded to slower (because of the inhibition of the right hemisphere induced by rTMS in healthy participants or a lesion in patients) and right-sided stimuli are responded to faster (because of the disinhibition of the contralateral hemisphere caused by right-hemisphere rTMS in healthy participants or a lesion in patients). Secondly, in line with what was observed with RTs, the power of the P200 component was found unchanged after rTMS while it was increased after the Sham (ineffective) stimulation protocol, thus indicating again an inhibitory effect of rTMS on a learning process induced by task repetition (see also the results obtained in the "Rest" session). Importantly for the present discussion and in line with RT results, this inhibitory effect occurred regardless of the side of presentation of visual stimuli. Again, this result argues against the predictions of the inter-hemispheric rivalry models. According to these models, indeed, the reduction of the amplitude of the P200 component induced by rTMS of the right parietal cortex is expected to be accompanied by an increase of the amplitude of the P200 component recorded over the left parietal cortex, due to the postulated release from inter-hemispheric inhibition. Contrary to this prediction, the present results revealed a comparable reduction of the amplitude of the P200 component recorded in both hemispheres after rTMS to the right hemisphere. In this respect, several studies in the literature suggested that the increment of posterior P200 amplitude is an index of "perceptual learning" due to an increase in neuronal sensitivity (Song et al., 2007), and it could be considered as the electrophysiological correlates underlying the learning effects observed in the reaction time during the post-stimulation detection task (Ding et al., 2003). More importantly, it has been shown (Di Russo et al., 2008) that the P200 component is delayed and/or reduced in amplitude for stimuli contralateral to the brain lesion in neglect patients and it has been interpreted as the evidence of a defective feedback modulation from higher areas on extrastriate and striate areas.

Taken together, these results do not confirm the predictions put forward by the inter-hemispheric rivalry models, i.e. as a result of a reduction of neural activity in the right hemisphere (due to TMS or a lesion) the contralateral hemisphere is disinhibited becoming hyper-activated. In the present experiment, what follows inhibition of the right hemisphere is a comparable inhibition of the contralateral hemisphere. This phenomenon resembles the well-known phenomenon of diaschisis described by Von Monakow (1914) and, specifically, the diaschisis commissuralis, that is the transcallosal down-regulation of neuronal activity in the interconnected contralateral hemisphere that follows an injury in one hemisphere. In the same vein, in the present paper we showed that the cortical inhibition induced by rTMS of the right parietal cortex, which simulates the hypo-activity induced by a lesion, produced a functional depression of the contralateral cortex through transcallosal diaschisis. According to this reasoning it follows that, contrary to the postulates of the inter-hemispheric rivalry models, the role of the corpus callosum is not that of maintaining the two hemispheres in a reciprocal inhibitory state. In this respect, callosal section models can be very informative in disentangling whether a right brain lesion causing neglect would induce contralateral facilitation or inhibition. Indeed, if the two hemispheres inhibit each other and neglect results from a left hemisphere hyper-activation due to the release of the reciprocal inhibition following a lesion in the right hemisphere, thus a clear prediction can be made: a callosal disconnection should ameliorate neglect symptoms. Contrary to this prediction, there is the so-called phenomenon of "callosal neglect" (Heilman and Adams, 2003). Several studies in the literature show the involvement of the corpus callosum in neglect. Firstly, studies investigating neglect in patients with right posterior cerebral artery infarction have shown that a concomitant lesion of the splenium of the corpus callosum can either cause spatial neglect (Park et al., 2006; Tomaiuolo et al., 2010) or mediate its severity (Bird et al., 2006). Secondly, it has been found (Bozzali et al., 2012) that microstructural damage of the posterior part of the corpus callosum, as measured with diffusion imaging and tract-based spatial statistics, determines the presence and the severity of spatial neglect. Thirdly, a section of the posterior part of the corpus callosum one year after a right hemisphere lesion not showing any signs of spatial neglect, abruptly induced it (Heilman and Adams, 2003). In this respect, the assumption of opponent processes in the two hemispheres exerting a reciprocal inhibition seems to be an oversimplification of the relationship between complex structures within the cerebral hemispheres (Berlucchi, 1983) and it is not supported by the previously reported pieces of evidence. Accordingly, it is important to note that the concept of inter-hemispheric dynamics has evolved (e.g. Corbetta and Shulman, 2002) since the model proposed by Kinsbourne (1977) by taking into account the role played by the ventral and dorsal parietal areas by themselves and the interplay between them both within the same hemisphere and between the two hemispheres. Indeed, in addition to the ventral parietal cortex being relevant for spatial cognition, such kind of evidence has been reported also for the dorsal parietal cortex: e.g. TMS over dorsal parietal areas in the right hemisphere has been found to elicit neglect-like or extinction-like signs in healthy participants (e.g., Thut et al., 2005; Dambeck et al., 2006; Cazzoli et al., 2009) and to modulate the inter-hemispheric competition in alpha-band coherence (Rizk et al., 2013). These data are in line with the findings by Corbetta et al. (2005) showing that the inter-hemispheric imbalance is observed between the DANs in the

two hemispheres (but see also Sasaki et al. (2013) reporting that the severity of neglect correlates with alpha-band inter-hemispheric connectivity in the left/right VANs while this was not the case in left/right DANs connectivity). Differently from these papers, here TMS was applied over the right ventral parietal area, i.e. the portion of the parietal cortex more directly related to spatial neglect, and no such inter-hemispheric imbalance has been found. In order to better assess the inter-hemispheric dynamics for both the left/right ventral and left/right dorsal parietal areas, future research should thus investigate, with the same TMS–EEG co-registration approach used here, whether the same or different results would be found if TMS is applied over the dorsal parietal areas.

Importantly, the results of the present paper and the data reported in the literature seem at odds with the several pieces of evidence showing hyperexcitability of the left hemisphere after a lesion to the right one (Koch et al., 2012) and the efficacy of rehabilitation protocols in neglect conceived at reducing the left hemisphere hyperactivity (Hesse et al., 2011; Oliveri, 2011; Müri et al., 2013). It must be noted, however, that both imaging studies showing hyperactivation of the left hemisphere and TMS studies inducing a regression of neglect symptoms by inhibiting the postulated left hemisphere hyperactivity were performed on patients in a subacute/chronic phase (i.e. several weeks after stroke). It is thus possible that plastic reorganization of functions could have already taken place. In this respect, the most striking evidence of the causal role of the left hemisphere hyperactivity is to find the same pattern of hemispherical imbalance in acute (within the first hours/days after stroke) neglect patients. Contrary to this prediction, however, several independent investigators using PET (Fiorelli et al., 1991; Perani et al., 1993) and SPECT (Vallar et al., 1988) have found that neglect patients in the acute phase (first days after stroke) showed a widespread hypo-metabolism (or reduced activation) both of right (damaged) and left (structurally intact) hemisphere, thus ruling out the presence, at the acute phase, of such a hemispherical imbalance. Interestingly, a more recent study with fMRI (Umarova et al., 2011) has found that in neglect patients in the acute phase (62.4 ± 8.1 h after stroke), this imbalance was not predictive of the presence or absence of neglect, although a left–right parietal imbalance after a right-hemispheric lesion was present, thus not being itself causative of neglect. Moreover, several studies (Vallar et al., 1988; Pantano et al., 1992; Perani et al., 1993; Pizzamiglio et al., 1998; Thimm et al., 2008; Cappa and Perani, 2010), investigating the neural correlates of recovery from acute neglect, found that functional recovery correlated with an improvement of the cortical metabolism not only in the structural unaffected areas in the right hemisphere but also in several areas of the left hemisphere.

The novelty of the present paper relies on the use of an off-line EEG–TMS interactive co-registration approach (Miniussi and Thut, 2010), which gave us the opportunity to directly test the effects of an inhibitory (Maeda et al., 2000; Valero-Cabrè et al., 2006) stimulation of the right parietal cortex, both on the cortical activity of the stimulated cortex and, more importantly, on that of functionally connected areas (Ilmoniemi et al., 1997; Miniussi and Thut, 2010; Bortoletto et al., 2015) in the left hemisphere, specifically the left parietal cortex. In this respect, we are conscious that a study with healthy participants cannot rule out theories on spatial neglect. However, we believe that the present results, together with the previously described papers with neglect patients, can pose the bases for a further investigation, with neglect patients, on whether hyperactivation of the left hemisphere is causative of spatial neglect, as suggested by the inter-hemispheric rivalry models, or alternatively reflects long-term maladaptive plastic reorganization following a brain lesion, as previous papers (Umarova et al., 2011; Ricci et al., 2012) and the present data seem to suggest.

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