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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 ($\leq$ 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