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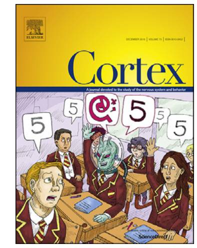

Research report

Theta burst stimulation improves overt visual search in spatial neglect independently of attentional load

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ABSTRACT

Visual neglect is considerably exacerbated by increases in visual attentional load. These detrimental effects of attentional load are hypothesised to be dependent on an interplay between dysfunctional inter-hemispheric inhibitory dynamics and load-related modulation of activity in cortical areas such as the posterior parietal cortex (PPC).

Continuous Theta Burst Stimulation (cTBS) over the contralesional PPC reduces neglect severity. It is unknown, however, whether such positive effects also operate in the presence of the detrimental effects of heightened attentional load.

Here, we examined the effects of cTBS on neglect severity in overt visual search (i.e., with eye movements), as a function of high and low visual attentional load conditions. Performance was assessed on the basis of target detection rates and eye movements, in a computerised visual search task and in two paper-pencil tasks. cTBS significantly ameliorated target detection performance, independently of attentional load. These ameliorative effects were significantly larger in the high than the low load condition, thereby equating target detection across both conditions. Eye movement analyses revealed

Abbreviations: ANOVA, Analysis of variance; cTBS, Continuous theta burst stimulation; iTBS, Intermittent theta burst stimulation; PPC, Posterior parietal cortex; rTMS, Repetitive transcranial magnetic stimulation; SEM, Standard error of the mean.

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that the improvements were mediated by a redeployment of visual fixations to the contralesional visual field.

These findings represent a substantive advance, because cTBS led to an unprecedented amelioration of overt search efficiency that was independent of visual attentional load.

1. Introduction

Visual neglect is defined as the failure to orient, attend, and respond towards the contralesional side of visual space (Heilman, Watson, & Valenstein, 1993). Visual neglect is most commonly associated with the incidence of a lesion within an extended network of cortical and subcortical areas centred in the right hemisphere (Corbetta & Shulman, 2011). Critical cortical areas include the posterior and inferior parietal lobe (Mort et al., 2003), the superior temporal lobe (Karnath, Fruhmann Berger, Küker, & Rorden, 2004), and the inferior frontal lobe (Husain & Kennard, 1996), whereas the main subcortical regions implicated in neglect include the pulvinar nucleus of the thalamus, the putamen, and the caudate nucleus (Karnath, Himmelbach, & Rorden, 2002). Moreover, disconnections of white matter fibre tracts also play an important role (Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), such as the superior longitudinal fasciculus, the inferior occipito-frontal fasciculus, and the superior occipito-frontal fasciculus (Karnath, Rorden, & Ticini, 2009; Shinoura et al., 2009).

A hallmark of visual neglect is that its' severity is significantly exacerbated by heightened visual attentional load, such as when discriminating visual targets from an increasing number of distracters (Bonato, 2012; Sarri, Greenwood, Kalra, & Driver, 2009). For instance, the same patient may perform within normal range in tests with low visual attentional load, but may show significant signs of visual neglect when assessed with tests with high visual attentional load.

There are two main reasons to predict that the modulation of activity in the posterior parietal cortex (PPC) is key to addressing the load-related modulation of neglect severity. First, the attentional networks of the left and the right hemisphere are centred around the parietal cortices, and compete to direct visual attention towards the contralateral side of space, thereby inhibiting each other via transcallosal connections (Koch et al., 2011). Lesions within the right-hemispheric attentional network lead to deficient inhibition towards the intact, contralateral left-hemispheric attentional network, and thus to pathological hyperexcitability (Baldassarre et al., 2014; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; He et al., 2007). The degree of hyperexcitability in the left, intact PPC has been shown to correlate with the degree of ipsilesional bias in the deployment of visual attention (Koch et al., 2008); namely, the greater the hyperexcitability in this area, the greater the neglect severity. Second, in healthy subjects, a heightened visual attentional load leads to a bilateral increase in neural activity within the attentional networks, including both left- and right-hemispheric PPCs (Schwartz et al., 2005). Moreover, the strongest, linear increase in neural activity with increasing visual attentional load occurs in both the left and the right PPCs (Jovicich et al., 2001). Hence, in patients with left-sided visual neglect due to a right-hemispheric lesion, a load-related increase in neural activity may occur only in the left, intact PPC. This would increase the existing hyperexcitability even further, and trigger a greater imbalance in inter-hemispheric inhibition, resulting in an exacerbation of visual neglect severity.

One of the key approaches to tackling this pathological hyperexcitability in the left, intact PPC has been to apply inhibitory, repetitive transcranial magnetic stimulation (rTMS), which ameliorates visual neglect symptoms (see for reviews Cazzoli, Müri, Hess, & Nyffeler, 2010; Hesse, Sparing, & Fink, 2011; Müri et al., 2013; Utz, Dimova, Oppenländer, & Kerkhoff, 2010). Importantly, the degree of behavioural amelioration correlates with the reduction in the hyperexcitability of the left, intact PPC (Koch et al., 2012). Up until now, however, it is unknown whether these positive effects of rTMS can also counteract the detrimental effects of heightened attentional load.

The aim of the present study was to investigate whether the repeated application of continuous theta burst stimulation (cTBS) – an inhibitory, patterned rTMS protocol (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Nyffeler et al., 2006) – would counteract the detrimental effects of heightened attentional load on visual neglect severity. We applied cTBS because this protocol seems to be particularly promising not only in decreasing the pathological hyperexcitability of the left, intact PPC, thereby ameliorating neglect symptomatology (Cazzoli et al., 2012; Fu et al., 2015; Hopfner et al., 2015; Koch et al., 2012; Nyffeler, Cazzoli, Hess, & Müri, 2009), but also in "stabilising and locking" the excitability of the stimulated area (Goldsworthy, Müller-Dahlhaus, Ridding, & Ziemann, 2015a). This latter aspect has the potential to prevent the exacerbation of neglect severity, which is associated with heightened visual attentional load.

We applied cTBS over the left, contralesional PPC in a group of neglect patients, under high and low visual attentional load conditions. We measured the effects of the intervention and its interaction with the varying visual attentional load by means of two approaches. First, we administered a computerised, on-screen search task, in which visual attentional load was directly manipulated and behavioural performance was assessed. Eye movements were measured during the task to assess whether the overt spatial allocation of attention (i.e., the distribution of visual fixations in space) was associated with the accuracy of visual target detection (cf. Karnath, Niemeier, & Dichgans, 1998; Malhotra, Coulthard, & Husain, 2006; Müri, Cazzoli, Nyffeler, & Pflugshaupt, 2009; Pflugshaupt et al., 2004; Sprenger, Kömpf, & Heide, 2002).