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Transcranial magnetic stimulation to dorsolateral prefrontal cortex affects conflict-induced behavioural adaptation in a Wisconsin Card Sorting Test analogue

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ABSTRACT

A substantial body of literature has proposed a role for dorsolateral prefrontal cortex (dlPFC) in supporting behavioural adaptation during conflict tasks. The vast majority of the evidence in support of this interpretation comes from neuroimaging studies. However, in order to unequivocally ascribe such a role to dlPFC, it is important to determine whether or not it is *essential* for this mechanism, and this can only be achieved by lesioning the area or interfering with its activity. In this study, we investigated the effects of repeated Transcranial Magnetic Stimulation (rTMS) to dlPFC on performance on a conflict version of a Wisconsin Card Sorting Test analogue (used previously in circumscribed lesion studies in monkeys) in neurologically healthy human participants. Our results supported the view of dlPFC as a fundamental structure for optimal conflict-induced behavioural adaptation, as stimulation cancelled out the adaptation effect normally observed on control trials. We show that there is some indication of differential modulation of trial types by stimulation and we hypothesize that this might suggest a role for dlPFC in conflict-induced adaptation that is more specifically concerned with the maintenance of conflict-history information online across trials.

1. Introduction

Dorsolateral prefrontal cortex (dlPFC – defined here as the region occupying Brodmann areas 46, 9/46 and 9 in the superior and middle frontal gyri) is believed to play a fundamental role in exerting top-down control on behaviour. One of the processes dlPFC has been strongly implicated in is the implementation of cognitive control to drive behavioural adaptation during tasks eliciting conflict between two (or more) competing responses. A classic conflict task is the Stroop task (Stroop, 1935), where participants are asked to name the colour a written word is printed in while ignoring the word itself, while conflict is manipulated by using colours congruent (e.g. 'Red' in red ink) or incongruent (e.g. 'Red' in green ink) with the written word.

In the presence of interference between competing responses (i.e. on high-conflict trials, H), subjects' performance is negatively affected compared to trials where responses do not interfere with one another (i.e. low-conflict trials, L), with a decrease in speed of response and/or accuracy (e.g. Eriksen and Schultz, 1979; Hedge and Marsh, 1975; Simon and Small, 1969; Simon, 1990; Stroop, 1935; van Veen and Carter, 2005). This is generally defined as a 'conflict cost' on performance and is measured as the difference in speed and/or accuracy between H and L trials.

In this context, behavioural adaptation is generally defined as a *reduction* in conflict cost after subjects have been already exposed to conflict on one (or more) immediately preceding trials (also referred to as 'Gratton effects' or 'sequential effects') (Chen and Melara, 2009; Gratton et al., 1992; Hommel et al., 2004; Nieuwenhuis and Stins, 2006; Ullsperger et al., 2005; Wühr and Ansorge, 2005). Adaptation effects are often attributed to a number of different mechanisms. For example, some accounts point to cognitive control mechanisms becoming engaged on H trials and from there on proactively counteracting the detrimental effects of conflict on subsequent trials by enhancing task-relevant - while suppressing task-irrelevant - information (e.g. Botvinick et al., 2001; Botvinick, 2007; Egner and Hirsch, 2005a). Other accounts emphasize the role of the maintenance of conflict-related information in working memory (Mansouri et al., 2007) in aiding adaptation, or the refreshing/retrieval of task instructions and rules (Badre, 2008; Raye et al., 2002; Roth et al., 2009). While adaptation is likely a result of all these different mechanisms operating in concert with one another, rather than due to one specific mechanism, one important question concerns the localization of these processes within the neural substrate.

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Imaging studies have reported high levels of dlPFC activation during adaptation trials in various types of conflict task, such as the Stroop (Egner and Hirsch, 2005a, 2005b; Kim et al., 2012, 2013), Simon (Kerns, 2006) and flanker (Durston et al., 2003) tasks and suggest a role for this area in supporting behavioural adaptation. While fMRI can provide correlational evidence for the role of a region in a specific cognitive process, neuropsychological studies are essential to determine whether that region is *necessary* for the process. Although neuropsychological evidence on the role of dlPFC in conflict-induced adaptation is currently rather scarce, one study using a conflict analogue of the Wisconsin Card Sorting Test (WCTS) in non-human primates has indeed shown that lesions to dlPFC, impair behavioural adaptation (Mansouri et al., 2007). These findings have also been replicated in human neuropsychological patients using the same task (Boschin et al., in press), and appear consistent with the neuroimaging literature.

Several issues, however, complicate the assessment of neuroimaging findings in neuropsychological patients. One crucial limitation is that, in the vast majority of human clinical cases and unlike the case of laboratory animals that undergo surgical lesions, brain damage is not localized exclusively to the region of interest and might involve, sometimes large, lesions to other brain areas. Furthermore, there is often no opportunity to collect pre-lesion data (which allows to assess the effects of brain damage on a process within-subjects), as well as relatively little control over the length of the period between the lesion and testing and possible compensations that might occur in that interim. One valuable, complementary methodology that can help overcome these limitations is Transcranial Magnetic Stimulation (TMS). TMS allows the experimenter to interfere with neural activity in the brain in a way that has often been described as a temporary 'virtual lesion' (Pascual-Leone et al., 1994; Walsh and Cowey, 2000; Walsh and Rushworth, 1999). In this study, we sought to investigate the effects of TMS to dlPFC on measures of conflict-induced behavioural adaptation in the conflict analogue of the WCST.

Several studies have previously used TMS to investigate the mechanisms underlying performance in conflict tasks. However, while areas such as the medial PFC (mPFC) (Hayward et al., 2004; Jin et al., 2010; Neubert et al., 2010; Soutschek et al., 2013; Taylor et al., 2007), pre-motor and motor cortices (Neubert et al., 2010; Praamstra et al., 1999; Stürmer et al., 2000) and posterior parietal cortex (Jin et al., 2010; Stürmer et al., 2007) have been commonly targeted, very few studies have looked at the effects of TMS on dlPFC, especially with regards to adaptation.

TMS to the dlPFC has been found to have no significant effect on conflict cost measures on the current trial (Vanderhasselt et al., 2007, 2006; Wagner et al., 2006), but, consistent with the neuroimaging data, it has been found to affect behavioural adaptation on the next trial. Sturmer and colleagues (2007) looked at effects of TMS to dlPFC on adaptation during a Simon task, and found that the reduction in conflict cost usually observed after high-conflict trials was abolished by 20 Hz repetitive TMS (rTMS) applied to the left dlPFC. To the best of our knowledge, this is the only study that has investigated the link between dlPFC and adaptation using TMS.

As previously mentioned, one of the most common explanations for conflict-induced adaptation is that, after cognitive control is engaged, task-relevant information is enhanced, the competing, task-irrelevant information is suppressed and thus the detrimental effect of conflict on performance is reduced (Botvinick et al., 2001; Botvinick, 2007). One would therefore expect that the reduction in conflict costs should involve an improvement in performance on high-conflict trials that were preceded by another high-conflict trial (i.e. HH trials) compared to high-conflict trials that were preceded by a low-conflict trial (i.e. LH trials). However, studies often do not specify whether this is the case (Chen and Melara, 2009; Stürmer et al., 2002; Wühr and Ansorge, 2005). In their investigation into the effects of TMS to dlPFC on adaptation, Sturmer and colleagues (2007) did indeed not specify whether the adaptation effect is abolished through the effects of TMS on specific trial sequences. This is however an important detail, as it can help elucidate what mechanisms are contributing to adaptation in a particular context, for example whether it is via the enhancement of task-relevant behaviour or, as it might be the case when adaptation effects that are entirely due to reductions in speed of response on low-conflict trials following high-conflict trials (i.e. HL trials) (e.g. Horga et al., 2011; Stoffels, 1996), through an increase in caution. Most importantly, as adaptation is likely due to a number of complementary mechanisms, specifying the effects of stimulation on specific trial types can help determine whether a region of interest is important for supporting one mechanism over another, and thus provide a more thorough account of how adaptation might emerge at the network level.

We know from previous work (see "Pilot Study" in the Supplementary Material section) that, in neurologically healthy populations, adaptation effects in the conflict analogue of the Wisconsin Card Sorting Test (WCST) are due to differences in the speed of responses on HH trials compared to LH trials (with faster responses on the former), and that low-conflict trials are unaffected by the nature of the previous trial (i.e. there is no difference in speed of response on HL compared to LL trials). We also know that lesions to dlPFC abolish this effect in both non-human (Mansouri et al., 2007) and human (Boschin et al., in press) primates. In the current study, we followed up on this work by investigating whether TMS to the dlPFC in neurologically healthy participants affects adaptation in the WCST analogue in a manner similar to lesions. Using a paradigm similar to Sturmer and colleagues' (2007), we applied on-line repetitive rTMS to the left dlPFC during selected trials. Most importantly, given the flexibility afforded by TMS to observe the effects of the 'virtual lesion' selectively on a proportion of HH and LH trials while leaving other HH and LH trials unaffected within-subjects, we were able to ask whether the adaptation effect is abolished via increase in speed on LH trials or decrease in speed in HH trials (or both).

We hypothesized that stimulation would abolish the adaptation effect normally observed on non-TMS trials, consistent with findings from lesion studies of dlPFC in monkeys and patients on this task (Boschin et al., in press; Mansouri et al., 2007), and with the human imaging literature suggesting a role for dlPFC in adaptation (Durston, 2003; Egner and Hirsch, 2005a, 2005b; Kerns, 2006; Kim et al., 2012, 2013). Furthermore, we hypothesized that, if the role of dlPFC in adaptation is to actively engage cognitive control or to enhance task-relevant information while suppressing task-irrelevant information (Botvinick, 2007; Botvinick et al., 2001; Egner and Hirsch, 2005a), HH trials (i.e. the trials that should most benefit from this type of proactive engagement of cognitive control), should be most affected by TMS, with response speed dropping to LH levels, therefore canceling out the adaptation effect. We would not expect LH trials to be affected by disruption to cognitive control mechanisms as a low level of control already characterizes these trials to begin with. On the other hand, if dlPFC is involved in maintaining information about recent conflict-history in working-memory across trials (Mansouri et al., 2007), LH and HH trials should both be affected by TMS, as response speed in both should be dependent on conflict-history. This is because the cognitive system should still be able to implement some degree of cognitive control, but not to efficiently modulate it on a trial-by-trial basis as if it had access to a full history of recent conflict. One hypothesis is that the cognitive system might 'reset' to an average level of control that might not be as 'lax' as it would normally be after low-conflict trials (thus speeding up LH responses) but not as high as it would normally be after high-conflict trials (thus slowing down HH responses). Alternatively, if dlPFC's role in these kinds of tasks is to refresh/retrieve task instructions and rules (Badre, 2008; Raye et al., 2002; Roth et al., 2009), we predict that LH trials should be most affected, becoming even slower, as these are the trials signaling the need to retrieve task instructions.

2. Materials and methods

2.1. Participants

32 participants (15 male, mean age 24.18 years) took part in the