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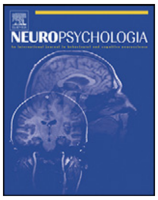

Double dissociation of working memory load effects induced by bilateral parietal modulation

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ABSTRACT

Transcranial magnetic stimulation and neuroimaging data have revealed bilateral posterior parietal cortex (PPC) involvement during verbal *n*-back working memory (WM). In this task as *n* (i.e., WM load) increases, subjects show poorer behavioral performance as well as greater activation of this brain area. Moreover, there is evidence that a brief period of practice or even increased familiarity with the task can improve WM performance and lead to activation changes in the PPC. The aim of this study was to investigate, using transcranial direct current stimulation (tDCS), the effects on WM load performance induced by different PPC modulation after increased familiarity with the task. After a short practice, we tested verbal WM using an *n*-back task (1-back vs. 2-back) before and after the application of bilateral tDCS over PPCs (left anodal-right cathodal, left cathodal-right anodal or sham). ANOVA showed a significant interaction between tDCS and task. In the 1-back task, left anodal-right cathodal modulation abolished improvement in reaction times observed in the other two modulation conditions. Conversely, in the 2-back task the same effect was observed after left cathodal-right anodal modulation relative to the other two modulation conditions. This double dissociation demonstrates either a differential engagement of each PPC or changes in the interhemispheric balance of activity across this brain region. Neuroimaging studies show parametric activation of the PPC as difficulty increases, but activation does not switch sides. Thus, our observed effects cannot be attributed to increased task difficulty, the stimuli used, or the response requirements. Rather, we suggest that these findings reflect the use of different processing strategies to perform these two tasks. In conclusion, after increased familiarity with the task, different tDCS modulations lead to changes in a task-related region depending on differences in processing strategies in 1-back vs. 2-back.

1. Introduction

It has been hypothesised that higher brain functions such as language, planning and problem solving rely on working memory (WM) i.e., a system that acts to temporarily maintain and manipulate task-relevant information (Baddeley, 1986; Just & Carpenter, 1992; Shallice, 1988). Several theories on WM have been proposed (for review see Miyake & Shah, 1999). At present the model proposed by Baddeley and Hitch (1974) is one of the most extensively investigated theoretical constructs of WM. The authors proposed the existence of three functional components of WM. A central executive was envisioned as a control system of limited attentional capacity that is responsible for the manipulation of information within WM and for controlling two subsidiary storage systems: a phonological loop, which is based on sound and language, and a visuospatial sketchpad. The phonological loop was assumed to be responsible for the storage and maintenance of information in a phonological form and consists of two parts: a short-term phonological store and an articulatory rehearsal component that can revive the memory trace. The visuospatial sketchpad was dedicated instead to the storage and maintenance of visual and spatial information. Based on a number of empirical findings a fourth component, the episodic buffer, was added (Baddeley, 2000). The episodic buffer is assumed to be a limited capacity store that is capable of multi-dimensional coding to allow the binding of information to create integrated episodes.

Regarding the neural substrates of WM, the dorsolateral prefrontal cortex (DLPFC) has been shown to be related to central executive processes (for review see Smith & Jonides, 1998). While

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Broca's area has been associated with the articulatory rehearsal component, the posterior parietal cortex (PPC) has been claimed to be the site that mediates the storage systems: the phonological loop and the visuospatial sketchpad (Baddeley, 2003; Jonides, Schumacher, et al., 1998; Smith, Jonides, Marshuetz, & Koeppe, 1998; Todd & Marois, 2004; Xu & Chun, 2006, but see Buchsbaum & D'Esposito, 2008 about the phonological loop). However, there is evidence that the functional neuroanatomy of WM may be more complex and anatomically distributed, with PPC playing a role also in the executive component (Cohen et al., 1997; Collette, Hogge, Salmon, & Van der Linden, 2006; Mottaghy, Doring, Muller-Gartner, Topper, & Krause, 2002).

A common task used to study WM is the "*n*-back" (Gevins & Cutillo, 1993), a task that has been designed to manipulate factors associated with WM such as load (Carter et al., 1998). In the most typical variant of this task, the participant is required to monitor a series of stimuli (e.g., letters) presented centrally and to respond whenever a stimulus that is the same as the one presented *n* trials previously is presented, where *n* is a pre-specified integer (usually 1, 2, or 3). As *n* increases, there is a greater demand on WM and consequently a poorer behavioral performance. Therefore, this task requires the simultaneous engagement of several retention- and control-related operations and is therefore assumed to place great demands on a number of key processes within WM.

In recent years, variants of the n-back procedure have been employed to investigate the neural basis of WM processes. Neuroimaging (Owen, McMillan, Laird, & Bullmore, 2005) and transcranial magnetic stimulation (Mottaghy et al., 2002; Mottaghy, Gangitano, Krause, & Pascual-Leone, 2003; Mottaghy, Pascual-Leone, et al., 2003) studies have shown that in addition to the contribution of prefrontal cortex (PFC), n-back studies have frequently demonstrated the involvement of PPC regions, particularly the superior and inferior parietal lobes (SPL, and IPL, respectively) (for reviews see Cabeza & Nyberg, 2000; Mottaghy, 2006; Owen et al., 2005).

Regarding the WM load, neuroimaging studies have reported frontal and parietal activity increases during 2-back relative to 1-back task performance as well as parametric variations of *n*. Specifically, the activated regions are common and activation does not switch sides with increasing difficulty (Braver et al., 1997; Cohen et al., 1997; Jonides et al., 1997a; Ragland et al., 2002). This increase in activation presumably reflects the augmented load on control processes devoted to holding items and temporal information in WM, and transient 'updating' of maintained representations (Smith & Jonides, 1999). Updating during the 2-back task constitutes several additional subcomponents that become more critical relative to 1-back, such as temporal coding and eliminating selective information from WM (Jonides et al., 1997b; Postle, Berger, Goldstein, Curtis, & D'Esposito, 2001). Inhibition, monitoring and selection processes should be crucial for the updating function and for keeping track of item order, but also in the implementation of interference resolution during source judgments involving recent context irrelevant items (e.g., items presented "2-back" in the 1-back task) (Badre & Wagner, 2005; D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998).

Regarding the laterality, verbal n-back tasks appear to activate a fronto-parietal network in the left hemisphere while spatial n-back tasks appear to activate a right hemisphere network (D'Esposito et al., 1998; Fiez et al., 1996), although this pattern is by no means unequivocal and bilateral activity often occurs in both type of tasks (Braver et al., 1997; Nystrom et al., 2000). For example, neuroimaging studies during verbal *n*-back have reported bilateral activation of PPC. While some researchers have attributed right parietal activity to the necessity of spatial processing in some verbal WM tasks (Clark et al., 2000; Honey, Bullmore, & Sharma, 2000; Salmon et al., 1996) others have attributed more domain-general functions to the right parietal lobe, such as selective attention, that may be required when performing verbal WM tasks (Chein, Ravizza, & Fiez, 2003; Jonides, Schumacher, et al., 1998; LaBar, Gitelman, Parrish, & Mesulam, 1999). Both domain-specific (i.e., spatial coding) and domain-general accounts of right parietal contributions to verbal WM are supported by the literature making it difficult to differentiate between them.

Moreover, there is evidence that 1-back task and 2 or 3-back task do not just differ in difficulty, but also in the strategies used to perform them. Specifically, it has been shown that during a verbal n-back task, subjects might use an "activation" strategy, in which they respond to each letter based on its familiarity, or an "update" strategy, in which more WM resources are involved because they have to actively maintain a list of the prior letters and update that list after each letter is presented (Lovett, Daily, & Reder, 2000). Recognition memory can be supported by both an undifferentiated, strength-like memory signal (usually referred to as familiarity), and by the retrieval of qualitative information about the episode such as contextual details (usually referred to as recollection) (Yonelinas, 2002). Performance in the n-back task is consistent with this familiarity and recollection account, in which 1-back task is based on familiarity while 2 or 3-back tasks are based more on recollection (Harbison, Atkins, & Dougherty, 2011). Regarding the neural substrates of these processes, there is evidence that they are characterized by different patterns of brain activity in frontal, parietal and medial temporal cortices (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Diana, Yonelinas, & Ranganath, 2007; Duarte, Ranganath, Winward, Hayward, & Knight, 2004; Skinner & Fernandes, 2007; Vilberg & Rugg, 2008). Additionally, there are findings showing that recollective memories are frequently observed more in the left hemisphere while familiarity based-traces more in the right hemisphere (Dobbins, Simons, & Schacter, 2004; Duarte, Ranganath, & Knight, 2005; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Kensinger, Clarke, & Corkin, 2003; Mitchell, Johnson, Raye, & Greene, 2004; Nolde, Johnson, & D'Esposito, 1998; Vilberg & Rugg, 2009).

Finally, a brief period of practice with a WM task can improve performance and modify underlying patterns of neural activation (Kelly & Garavan, 2005). Whereas some studies have reported an increased activation in the PPC following a small amount of practice on WM tasks (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005), others have found decreased activation (Garavan, Kelley, Rosen, Rao, & Stein, 2000). Furthermore, even increased familiarity with the task can improve WM performance and lead to activation changes in the PPC (Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010).

The aim of this study was to investigate, using bilateral transcranial direct current stimulation (tDCS), the effects on WM load performance induced by different PPC modulations after increased familiarity with the task.

tDCS is a non-invasive technique for modulating cortical excitability by constantly applying weak electrical current over time to enhance (anodal modulation) or reduce (cathodal modulation) the excitation of neuronal populations, with a maximal effect on the stimulated area beneath the electrodes (Nitsche et al., 2008; Priori, 2003; Utz, Dimova, Oppenlander, & Kerkhoff, 2010).

After a short period of time in which subjects practiced with the task to increase familiarity, we tested verbal WM using a verbal n-back task (1-back vs. 2-back). WM was tested before and after the application of bilateral tDCS over PPCs (left anodal-right cathodal, left cathodal-right anodal and sham) in a between-subject design. The application of this electrode montage allowed us to modulate activity in the left and right PPC in opposite directions simultaneously.