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Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: rTMS evidence

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Abstract

The functional organization of working memory (WM) in the human prefrontal cortex remains unclear. The present study used repetitive transcranial magnetic stimulation (rTMS) to clarify the role of the dorsolateral prefrontal cortex (dlPFC) both in the types of information (verbal *vs.* spatial), and the types of processes (maintenance *vs.* manipulation). Subjects performed three independent experiments (1-back and 2-back tasks) while rTMS was applied over dlPFC for 500 ms in the last period of the delay. In two experiments (1 and 2) physically identical stimuli (letters shown at different locations on a screen) under different domain conditions (letters or locations) were employed. Under these conditions, we discovered a double dissociation only in the 2-back task: during the letter condition, when applied to the right dlPFC, rTMS significantly delayed task performance, whereas, the same result was present during the location condition, but only when rTMS was applied to the left dlPFC. The other 2-back task (experiment 3), in which we had eliminated the task-irrelevant information (i.e. we used stimuli that varied only in one domain), did not show significant results. We propose that the functional dichotomy of the hemispheres may be due to mechanisms of cognitive control on interference, which resolve conflict through the inhibition of task-irrelevant information only during high WM load. In conclusion, these findings confirm the role of dlPFC in implementing top-down attentional control, and provide evidence for the theoretical suggestion that working memory serves to control selective attention in the normal human brain.

Keywords: Dorsolateral prefrontal cortex (dlPFC); Lateralization; Working memory; Inhibition; Repetitive transcranial magnetic stimulation (rTMS)

1. Introduction

It has been hypothesized that higher brain functions such as language, planning and problem-solving rely on working memory (WM), i.e., a system which acts to temporarily maintain and manipulate task-relevant information (Baddeley, 1986; Just & Carpenter, 1992; Shallice, 1988).

According to Baddeley (1986, 2000), working memory is represented by a central executive that controls information in three storage buffers (the phonological loop, the visuo-spatial sketchpad and the episodic buffer) that act as a workspace for the storage and manipulation of information.

Evidence from neurophysiological (Fuster, 1989; Goldman-Rakic, 1987), neuropsychological (Shimamura, 1994; Stuss, Eskes, & Foster, 1994), functional neuroimaging (see Fletcher & Henson, 2001, for a review) and single or repetitive transcranial magnetic stimulations (rTMS) (see Mottaghy, 2006, for a review) studies supports a role of the prefrontal cortex (PFC) in a wide variety of WM tasks. Nevertheless, even if PFC has been identified to play a key role in WM, till now there is no consensus on its functional organization in humans (Cabeza & Nyberg, 2000; Duncan & Owen, 2000). Investigators have raised the question of whether different PFC regions subserve different functional processes

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and/or different types of information. It has been suggested that dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC) are associated, respectively, with manipulation/monitoring and maintenance/inhibition (D'Esposito, Postle, & Rypma, 2000; Owen, Evans, & Petrides, 1996; Petrides, 2000), or with spatial and non-spatial information (D'Esposito et al., 1998; Goldman-Rakic, 1987, 1995; Haxby, Petit, Ungerleider, & Courtney, 2000). It has also been suggested that left and right PFCs are associated, respectively, with verbal and non-verbal information (Smith & Jonides, 1997), or that PFC is functionally organized by both process and type of information (Johnson, Raye, Mitchell, Greene, & Anderson, 2003).

However, a recent alternative perspective portrays "working memory as a property that arises through the coordinated recruitment, via attention, of brain systems that have evolved to accomplish sensory-, representation-, or action-related functions". One corollary of this emergent process view is that the contribution of PFC to working memory does not include the temporary storage of information (see Postle, 2006, for a review). Evidence from TMS studies supports this point showing that delay-period rTMS does not disrupt storage of verbal (Feredoes, Tononi, & Postle, 2007; Postle et al., 2006) or spatial (Hamidi, Tononi, & Postle, 2006) information. In particular, in one of these studies (Postle et al., 2006) subjects were presented two types of trials in random order in which they were required to either (1) maintain a sequence of letters across a delay period or (2) manipulate (alphabetize) this sequence during the delay in order to respond correctly to a probe. Their two-step procedure entailed first, acquiring fMRI data and second, delivering rTMS to fMRI-identified areas of the dlPFC and superior parietal lobe while the same subjects performed the same task. Although, rTMS of the dlPFC selectively disrupted manipulation, rTMS of the superior parietal lobe disrupted manipulation and short-term retention at the same extent. In conclusion, their findings are consistent with the view that dlPFC contributes more importantly to the control of information in working memory than to its short-term retention.

As it can be seen in many studies investigated the cortical structures activated in WM paradigms and tried to disentangle areas involved in the different aspect of these tasks like sensory analysis, temporary storage, retrieval and action programming. Nevertheless, results are highly contradictory about the role of the PFC. This is also due to the fact that until now many studies have used physically different stimuli for spatial and object/verbal WM tasks, and this has introduced some difficulties into the data interpretation process. Such approach might be problematic, since it cannot reliably distinguish between perceptual stimulus effects and domain-related processes *per se*.

It is generally assumed that using physically identical stimuli and only varying instructions is the best way to rule out confounding factors in an experiment and as a result we can convincingly attribute differences in activation to WM processes. However, doing so, might actually introduce a new confound in that it might require inhibition of attention to variation in the irrelevant domain.

Recently, Ellis, Silberstein, and Nathan (2006) have examined the temporal dynamics of the spatial WM *n*-back task using steady state visual evoked potentials. Authors identified three different time periods of significance during the spatial *n*-back task—an early perceptual/encoding period (approximately 0–500 ms), an early delay period just following the stimulus disappearing from view (approximately 850–1400 ms), and a late period lasting the final second of the delay and anticipation of the new stimulus (approximately 2500–3500 ms). However, the main finding of this study was that the delay period was associated with two relatively distinct electrophysiological stages. In particular, during the last second of the delay period, both amplitude and latency were reduced. Although, the functional significance of such amplitude reduction in the late delay period is unknown, prefrontal amplitude reductions have previously been associated with cognitive set changes during the Wisconsin card sort test, a well-known test of executive function (Silberstein, Ciorciari, & Pipingas, 1995). Therefore, such reductions suggest that the frontal cortex is reallocated to executive (non-maintenance) aspects of the task (which may include manipulation of information, response preparation and anticipation of the new stimulus).

In order to clarify the influence of both the types of information (verbal *vs.* spatial) and the types of processes (maintenance *vs.* manipulation) in WM, we performed two independent experiments (1-back and 2-back). Both experiments used variants of the *n*-back task and involved physically identical stimuli (letters shown at different locations on a screen) for the different domain conditions (letters or locations). Regarding the type of process, although the mechanisms underlying "maintenance" and "manipulation" in our conceptual framework remain somewhat underspecified at present, we expect that the 1-back task will be classified as a maintenance task, and that a 2-back task will be seen as involving manipulation in addition to maintenance.

Regarding our task, the last second of the delay period could also be critical for executive aspects of the task, such as the inhibition of task-irrelevant information. Therefore, in order to test this suppression hypothesis we compared two different 2-back tasks (stimuli varied in both domains *vs.* stimuli varied only in one).

By means of repetitive rTMS, we decided to investigate the contribution of the dlPFC in these WM tasks. By inducing brief electric currents circulating within the brain areas immediately beneath the coil, rTMS provides the unique opportunity of transiently and non-invasively manipulating the brain activity of selected neural networks as an independent variable and, therefore, of investigating their influence on the performance of different cognitive tasks within a controlled experimental design. Imaging studies can reveal the brain regions which are active during the execution of a given task, but not which areas are essential for the performance of that task. With rTMS it is possible to interact with specific cortical areas at specific in time epochs, so that it can be used to establish the role of a given brain region in a particular task.

In the present study, rTMS was applied on target scalp areas (right and left dlPFCs) for 500 ms at the end of the delay period of the task. Thus, varying WM load and matching this with the stimulus properties, it was possible to identify the influence