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Working memory capacity in schizophrenia: a parametric fMRI study

J.M. Jansma[a], N.F. Ramsey[b,*], N.J.A. van der Wee[b], R.S. Kahn[b]

[a] *Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Stroke, NIH, 10 Center Drive, Bldg. 10, Room B1D118 MSC1065, Bethesda, MD 20892, USA*

[b] *Functional Imaging Section, Department of Psychiatry, Neuroscience Division, University Medical Center Utrecht, Room HP A01.126, P.O. Box 85500, 3508 GA Utrecht, The Netherlands*

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Abstract

Impaired working memory (WM) function in schizophrenia has been associated with abnormal activation of the dorsolateral prefrontal cortex (DLPFC). It is, however, not clear whether abnormal activation is a sign of DLPFC pathology, or a correlate of poor performance. We address this question by examining activity in the WM brain system at different levels of task difficulty. A parametric fMRI paradigm is used to examine how the WM system responds to increasing load.

A parametric fMRI design with four levels of a spatial *N*-back task was used to examine the relationships between working memory load, functional output (performance) and brain activity in 10 schizophrenic patients on atypical antipsychotic medication and to compare these to 10 healthy controls. In spite of increasingly poor performance in schizophrenic patients, activity increased normally in DLPFC and inferior parietal cortex bilaterally and in anterior cingulate, with increasing load. At 3-back, activity dropped in DLPFC in comparison with controls, but not in the other regions.

The results indicate that peak activation of the WM-system is reached at a lower processing load in schizophrenic patients than in healthy controls. As a decline of DLPFC activity at high processing loads in itself is not abnormal, WM dysfunction in schizophrenia appears to be the result of an impaired functional output of the whole WM system, causing elevation of the effective burden imposed by WM tasks.

Keywords: Schizophrenia; fMRI; Functional imaging; Working memory; Prefrontal cortex; *N*-back task

1. Introduction

Cognitive impairment is regarded as an important and basic characteristic of schizophrenia (Heinrichs and Zakzanis, 1998; Nuechterlein and Dawson, 1984; Heinrichs and Zakzanis, 1998). One system that has been hypothesized to play a major role in the cognitive deficits in schizophrenic patients is the working memory system (Goldman Rakic, 1994). Working memory is generally defined as a capacity-limited system for storing and manipulating information for short periods of time (Baddeley, 1992). The neural substrate of working memory has been examined in many imaging studies and has been related to activa-

* Corresponding author. Tel.: +31-30-250-6025; fax: +31-30-250-5443.
E-mail address: n.ramsey@azu.nl (N.F. Ramsey).

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tion of prefrontal (d'Esposito et al., 1995, 1999), parietal (Jonides et al., 1998) and anterior cingulate regions (Carter et al., 1999). Several imaging studies have specifically associated dorsolateral prefrontal (DLPFC) regions with the limited capacity for information processing of working memory (Callicott et al., 1999; Braver et al., 1997). In line with these results, it has been hypothesized that reduced engagement of the prefrontal cortex may be central to the cognitive problems of schizophrenic patients (Weinberger et al., 1986, 1992). Reduced activation of the prefrontal cortex in schizophrenic patients has been demonstrated with imaging studies during cognitive tasks, such as tasks involving verbal fluency (Curtis et al., 1998, 1999; Mellers et al., 1998; Yurgelun Todd et al., 1996), the Wisconsin card sorting task (Volz et al., 1997), learning of word lists (Hazlett et al., 2000) and verbal working memory tasks (Carter et al., 1998; Perlstein et al., 2001; Manoach et al., 2000).

Recent imaging studies, however, have reported normal or even increased activation of the prefrontal cortex in schizophrenic patients (Callicott et al., 2000; Frith, 1995;Manoach et al., 1999, 2000, 2001; Ramsey et al., 2002) using cognitive tasks that could be performed adequately by schizophrenic patients. Also, we have recently shown enhanced activation in medication-naive patients on a logical reasoning task when performance differences with control subjects are corrected for (Ramsey et al., 2002), suggesting that functional output of the WM system was reduced. These results indicate that the association of the prefrontal cortex with cognitive deficits in schizophrenic patients is more complex than initially was assumed.

The problem in studies on working memory that compare schizophrenic patients to controls is that the two groups often differ in performance (Ramsey et al., 2002; Perlstein et al., 2001). Tasks are generally based on neuropsychological applications, where it is important to show a difference in performance. Given that patients perform normal when tasks are easy, poor performance at demanding tasks may be indicative of impaired processing capacity. This in turn implies that when schizophrenic patients and controls are compared on one particular task, performance of the patients could be similar to what healthy subjects would display if the task was more demanding. The key question is whether in schizophrenia the response of the brain to capacity-exceeding demands on working memory is normal (albeit at a lower load than in controls), or abnormal.

Functional imaging provides an opportunity to address the question whether selective dysfunction of DLPFC can explain impaired working memory, or whether this impairment is associated with effects of schizophrenia on the WM system as a whole. For this purpose, a parametric experimental design can be used, where subjects perform several levels of a task, which differ on one parameter. The advantage of a parametric design is that it allows for assessment of the relationship between regional brain activity and functional output. Several studies combining functional magnetic resonance imaging (fMRI) with a parametric design have indicated that there is a positive correlation between activity in DLPFC and load on the working memory system (WM-load) provided that performance is well above chance (Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000). Although various investigators have used *N*-back tasks to study schizophrenic patients, only a few have fully exploited the parametric features. Callicott et al. (2000) compared schizophrenic patients selected for good performance to controls on a limited range of loads on a spatial *N*-back task, and found enhanced activity in right prefrontal and parietal cortex, and in left anterior cingulate, indicating reduced physiological efficiency. Differences in WM capacity could not be tested, as the range did not include a load at which capacity was exceeded.

Using a verbal *N*-back task with also three loads, Perlstein et al. (2001) reported that in schizophrenic patients the right DLPFC evinced a drop in activity at their highest load relative to controls, whereas other regions behaved normal. Again, performance was near-normal at all loads, precluding a test of WM capacity. Both studies utilized voxel-wise analysis of load and illness effects to identify regions. This approach is powerful in searching for regions where illness and load effects interact, but it does not compare different regions directly. If some regions exhibit a significant effect at the predetermined statistical threshold, and others do not, that does not prove that the latter are not affected. They may exhibit an effect that fails to meet the high threshold associated with map analysis (type II error). This problem can be overcome by testing for effect in a limited set