



Parietal cortex and episodic memory retrieval in schizophrenia

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ABSTRACT

People with schizophrenia consistently show memory impairment on varying tasks including item recognition memory. Relative to the correct rejection of distracter items, the correct recognition of studied items consistently produces an effect termed the old/new effect that is characterized by increased activity in parietal and frontal cortical regions. This effect has received only scant attention in schizophrenia. We examined the old/new effect in 15 people with schizophrenia and 18 controls during an item recognition test, and neural activity was examined with event-related functional magnetic resonance imaging. Both groups performed equally well during the recognition test and showed increased activity in a left dorsolateral prefrontal region and in the precuneus bilaterally during the successful recognition of old items relative to the correct rejection of new items. The control group also exhibited increased activity in the dorsal left parietal cortex. This region has been implicated in the top-down modulation of memory which involves control processes that support memory-retrieval search, monitoring and verification. Although these processes may not be of paramount importance in item recognition memory performance, the present findings suggest that people with schizophrenia may have difficulty with such top-down modulation, a finding consistent with many other studies in information processing.

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1. Introduction

Episodic memory shows significant impairment in people with schizophrenia, and great effort has been put forward to identify potential cognitive processes that could be selectively affected in schizophrenia. Several reviews of published studies have begun identifying conditions that modulate episodic memory performance in this population. It has been established (Aleman et al., 1999) that free recall and cued-recall memory tasks usually lead to more severe memory impairment in schizophrenia than tests of recognition memory. Recognition memory does nonetheless lead to significant memory impairments as another meta-analysis demonstrated (Pelletier et al., 2005).

At the same time, work in the field of cognitive neuroscience and functional neuroimaging has significantly contributed to our understanding of the cognitive architecture of episodic memory and its neural correlates, in particular for recognition memory which is more easily amenable to the imaging setting than recall. This knowledge is critical, as it provides us with a diversity of well-defined systems and processes that can be differentiated and used to identify both memory and brain dysfunctions in schizophrenia. The old/new effect, observed during recognition memory and described below, is one such example

of the contribution of functional neuroimaging to theories of episodic memory. This old/new effect refers to enhanced neural activity in multiple prefrontal and parietal cortical regions during the correct identification of a target (Kapur, 2003) relative to the correct rejection of a distractor. This effect could represent the neural correlates of retrieval success and/or post-retrieval processes (Rugg and Henson, 2002). Surprisingly, it has received only scant attention in schizophrenia research so far, although it represents a robust phenomenon that is easily observable in recognition memory studies.

The old/new effect has been observed both with event-related potentials (ERPs) and with event-related functional magnetic resonance imaging (fMRI), and has produced a very robust and reproducible pattern of activity that includes the medial and lateral regions of the posterior parietal cortex and the left prefrontal cortex (Rugg and Henson, 2002). This effect was initially interpreted as reflecting “retrieval success”, the actual recovery of information from memory (Rugg et al., 1996; Wilding, 1999; Konishi et al., 2000; McDermott et al., 2000). Subsequent studies suggested that the old/new effect could also represent other post-retrieval processes such as monitoring and verification (Rugg and Wilding, 2000; Achim and Lepage, 2005). The old/new effect typically leads to significant activations in the anterior part of the prefrontal cortex (BA 10) bilaterally (Henson et al., 2001; Rugg and Yonelinas, 2003) and the left dorsolateral prefrontal (BA 9/46). The stronger and more consistent neural correlates of the old/new effect are located in the posterior part of the parietal cortex. Recent neuroimaging evidence suggests that a constellation of separate functional areas in the region

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are more active during the retrieval of old information (Wagner et al., 2005). Among these areas are the precuneus and the retrosplenial cortex bilaterally, and the left lateral parietal cortex. Interestingly, this lateralization of activity in the lateral parietal cortex is independent of the nature (verbal or figural) of the material (Guerin and Miller, 2009) or perceptual modality (Shannon and Buckner, 2004).

While several studies have examined the neural activity of schizophrenia subjects during retrieval of old stimuli against a non-episodic memory control condition (be it rest or null events (Wiser et al., 1998; Barch et al., 2002; Hofer et al., 2003a,b; Jessen et al., 2003)), only a few have specifically examined the old/new effect. Using positron emission tomography (PET), a technique that cannot discriminate between correct and incorrect responses within a scan, Heckers et al. (2000) found a similar pattern of results when recognition of old stimuli was contrasted with the recognition of new stimuli. Ragland et al. (2004) reported a pattern of more diffuse activations in schizophrenia subjects, with patients showing over-activation in several areas, notably the orbitofrontal cortex (BA 11), left middle prefrontal cortex (BA 8), and right inferior parietal lobule (BA 40). In both studies, schizophrenia subjects performed significantly worse than healthy subjects, leaving open the possibility that, in the absence of clear and focal signals of retrieval success, schizophrenia subjects engage a more diffuse set of brain areas which could partly compensate and lead to the retrieval of past episodic information. In a more recent study, Ragland et al. (2006) examined the neural correlates of recognition without recollection contrasted with detecting new items. Both healthy controls and people with schizophrenia exhibited increased activity in parietal and frontal areas typically observed during the old/new effect. However, no analyses examined activations common to both groups. Finally, two ERP studies examined the old/new effect in people with schizophrenia. A study by Kayser et al. (1999) using word recognition memory found lower performance in the schizophrenia group relative to a healthy control group. Interestingly, at the neuronal level, both groups showed the old/new effect with greater late positivity to correctly recognized old words at posterior parietal sites. Another ERPs study by Tendolkar et al. (2002) examined the old/new effect during a recognition task in which old items had to be categorized with the Remember/Know procedure (Tulving, 1985), finding differences mainly in the frontal areas, with the patient group exhibiting a more widespread activation. Taken together, these results suggest that the old/new effect in schizophrenia remains equivocal and requires an investigation in which both patient and control groups perform equally well on a task that involves a simple binary decision (e.g. old or new).

The present study examined the old/new effect in a group of people with schizophrenia. As part of a larger study on memory and schizophrenia, a group of 40 schizophrenia subjects underwent an exhaustive clinical evaluation and a battery of cognitive test that included multiple measures of episodic memory. Of this sample, we selected a subgroup of patients who had above average memory performance, currently had relatively mild positive and negative symptoms, and who were able to function relatively well for the fMRI component of this study. Specifically, we selected patients who performed well on standardized measures of verbal and non-verbal episodic memory, and on an experimental task involving associative and item recognition memory. This selection was motivated by several factors, notably to minimize the between-group difference of performance during the item-based recognition memory test in the current imaging study, enabling us to exclude suboptimal performance as a potential explanation for differences in the pattern of neural activity. In addition, and considering our use of an event-related fMRI design, we wanted to make sure that our schizophrenia participants could perform our memory tasks above chance level. We also directly tested which brain areas are commonly active in both schizophrenia and healthy samples by conducting conjunction

analyses across groups. Based on the findings of Callicott et al. (2003) showing increased prefrontal activity under conditions of normal performance in schizophrenia, we hypothesized that the old/new effect would be associated with an increased activity (notably in the left prefrontal cortex) in the patient group relative to the healthy controls.

This study was part of a larger study comparing item recognition with association recognition, and the latter has been published elsewhere (Lepage et al., 2006).

2. Materials and methods

The protocol was approved by the institutional review boards of the Montreal Neurological Institute and the Douglas Institute. All participants were informed of the study procedure and provided full consent.

2.1. Subjects

Forty outpatients with DSM-IV-defined schizophrenia completed the behavioral and scanning procedures. Patients were recruited from the outpatient clinics of the Douglas Hospital. Clinical psychiatrists made the initial diagnosis, which was confirmed after the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (First et al., 1998). Overall, they were chronic patients, with mean duration of illness of 13.6 (S.D. \pm 9.5) years, as defined by the number of years since the onset of clinical symptoms as determined by the treating clinicians. Patients were clinically stable for at least four weeks and had been on a fixed medication regimen for at least six weeks before the initial evaluation. These forty participants received an exhaustive clinical assessment, a standardized neuropsychological assessment, and completed an experimental associative and item recognition memory recognition test. From this sample of 40 subjects with schizophrenia, 16 were selected to participate in the functional MRI component of this study. We selected these participants while considering memory performance, psychopathology, and level of functioning. In particular, and as mentioned in the Introduction, we were looking for schizophrenia subjects with relatively good performance on episodic memory tasks, namely on the Rey Auditory-Verbal Learning Task (Rey, 1964), the Rey Figure (Rey, 1959), and on an experimental associative and item recognition memory task described elsewhere (Luck et al., 2009). From this subsample of 16 schizophrenia subjects, all but one were taking antipsychotic medication: nine were on second-generation antipsychotics, four on conventional antipsychotics, and one was taking a combination of both. The mean dose of medication was equivalent to 328 mg/day of chlorpromazine (Woods, 2003). None of the patients had a concurrent mood disorder at the time of the study, though four patients were receiving concomitant antidepressant medication (mean dose equivalent to 50 mg of liquid fluoxetine) and one patient was taking a mood stabilizing medication. No patients were using benzodiazepines.

Eighteen healthy control subjects were recruited through advertisements placed in local newspapers, and examined with the Non-Patient Edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1998) to rule out current or past Axis I psychiatric disorders. Healthy subjects were selected to match the patients based on their sex, age, education, and primary language.

All participants were screened to exclude subjects with past or current head traumas or neurological disorders, family history of hereditary neurological disorders, current drug abuse, or any previous experiences of claustrophobia. Participants also conformed to standard health and safety regulations regarding the use of MRI (e.g., no metallic implants in their bodies, etc). For all participants, handedness was assessed with the Edinburgh Inventory (Oldfield, 1971).

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