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Abnormal prefrontal and parietal activity linked to deficient active binding in working memory in schizophrenia

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ABSTRACT

Working memory deficits have been widely reported in schizophrenia, and may result from inefficient binding processes. These processes, and their neural correlates, remain understudied in schizophrenia. Thus, we designed an FMRI study aimed at investigating the neural correlates of both passive and active binding in working memory in schizophrenia. Nineteen patients with schizophrenia and 23 matched controls were recruited to perform a working memory binding task, in which they were instructed to memorize three letters and three spatial locations. In the passive binding condition, letters and spatial locations were directly presented as bound. Conversely, in the active binding condition, words and spatial locations were presented as separated, and participants were instructed to intentionally create associations between them. Patients exhibited a similar performance to the controls for the passive binding condition, but a significantly lower performance for the active binding. FMRI analyses revealed that this active binding deficit was related to aberrant activity in the posterior parietal cortex and the ventrolateral prefrontal cortex. This study provides initial evidence of a specific deficit for actively binding information in schizophrenia, which is linked to dysfunctions in the neural networks underlying attention, manipulation of information, and encoding strategies. Together, our results suggest that all these dysfunctions may be targets for neuromodulation interventions known to improve cognitive deficits in schizophrenia.

1. Introduction

Schizophrenia (SZ) is associated with severe cognitive deficits, such as attention, memory and executive function (Heinrichs and Zakzanis, 1998; Saykin et al., 1991), which are among the most critical determinants of quality of life and level of function in patients (Green, 2006; Sharma and Antonova, 2003). Impairments of working memory (WM) – the system that transiently holds and manipulates information in the mind – are particularly prominent in SZ (Park and Gooding, 2014), and are considered as a cardinal feature of the illness (Barch and Ceaser, 2012; Goldman-Rakic, 1994). Researches revealed WM deficits across different tasks, stimuli modalities, or temporal components of events (Park and Gooding, 2014). One aspect of WM dysfunction that has received limited attention is the complexity of information processed, dissociating discrete (or unimodal) from bound (or multimodal) stimuli. For instance, it has been suggested that patients with SZ have more difficulties memorizing the association between information (multimodal) than the information itself (unimodal) (Burglen et al., 2004). This associative process, usually referred to as binding, may be of great importance in SZ, as its disturbance might induce incomplete or inaccurate representations (Mitchell and Johnson, 2009). Recently, we investigated WM binding in SZ in a set of complementary studies (Luck et al., 2008, 2009, 2010), in which participants were instructed to maintain items composed of letters and spatial locations, presented either bound or separated. We established that, when controlling for memory load and for spatial WM performance, patients performed equally well as controls for the binding condition, thus suggesting preserved binding capacities in patients (Giersch et al., 2011; Luck et al., 2008, 2009, 2010). This was recently confirmed by a meta-analysis on data from 301 patients with SZ and 237 healthy controls (Grot et al., 2014).

Noteworthy, most experimental assessments in SZ are based on passive binding, as information is presented as already bound, and hence less is known about active binding and its neural correlates in these patients. In everyday life, information processing also occurs with conscious efforts to associate things (e.g. stimuli, events and thoughts), in order to create a unified and coherent representation in memory. Consequently, the assessment of such active binding could provide a

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crucial missing part for a complete portrait of WM functioning in SZ. Active binding requires different cognitive operations, such as selective attention (Luck and Gold, 2008; Nuechterlein et al., 2015), manipulation of information (Gooding and Tallent, 2004; Kim et al., 2004), and encoding strategies (Bonner-Jackson and Barch, 2011; Bonner-Jackson et al., 2005), which are attributed to prefrontal and parietal functioning (Prabhakaran et al., 2000; Shafritz et al., 2002; Wendelken et al., 2008).

To the best of our knowledge, active binding and its neural correlates have not been investigated so far in SZ. Thus, we designed an experimental protocol that examined both passive and active forms of binding in WM in SZ. To identify possible finer cerebral dysfunctions in SZ, we used an event-related FMRI design that allowed assessment of encoding, maintenance, and retrieval processes. Based on our previous findings, we hypothesized that patients with SZ would exhibit preserved performance for passive binding, but altered performance for active binding. At the neural level, we anticipated that the specific active binding deficit would be linked to aberrant activity in prefrontal and parietal cortices that support cognitive processes required for active binding, such as attention, manipulation of information, and encoding strategies.

2. Material and methods

2.1. Participants

Demographic and clinical data are summarized in Table 1. Nineteen outpatients and 23 healthy controls participated in the study. All patients met the DSM-IV-TR criteria for schizophrenia (APA, 2000), based on the Structured Clinical Interview for DSM-IV (First et al., 2002). Symptom severity was determined using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients were clinically stable for at least one month at the time of testing. Seventeen patients were taking 2nd generation antipsychotic medication, one patient was taking 1st generation antipsychotic medication, and one patient was taking both types of medication. The healthy controls were recruited by means of advertisements placed in local newspapers. Controls were excluded if they reported current or past history of any Axis I disorders, neurological diseases, head trauma causing loss of consciousness, or if a first-degree family member had sought help for mental health issues or received a psychiatric diagnosis. The patient and control groups were matched on age, gender, handedness, parental socio-economic status, but had significantly different IQ[1] (see Table 1). The Regroupement Neuroimagerie/Québec Ethical Review Board approved the study. All participants signed an informed consent form prior to the experiment and received financial compensation for their participation.

Table 1
Sociodemographic and clinical data in patients with schizophrenia (SZ) and in controls. All data are presented as means and SEMs.

Characteristic	Patients with SZ N = 19	Controls N = 23	Analysis (P)
Sociodemographic characteristics			
Age (years)	36.30 (1.70)	32.78 (2.52)	0.20
Gender (M/F)	14/5	15/8	0.55
Handedness[a]	0.84 (0.05)	0.78 (0.11)	0.63
Parental SES score[b]	51.88 (3.31)	45.83 (4.60)	0.28
IQ[c]	96.21 (2.93)	105.18 (2.29)	0.02
Clinical characteristics			
Antipsychotic dose[d]	349.76 (47.26)		
PANSS Positive	16.16 (1.18)		
PANSS Negative	15.89 (0.90)		
PANSS General	34.38 (2.04)		

[a] Edinburgh Handedness Inventory.
[b] Hollingshead Parental Socio-Economic Status.
[c] Evaluated with the WAIS-III.
[d] Expressed in CPZ equivalent.

2.2. Procedure

Prior to scanning, participants were provided with a detailed description of the task, followed by a short practice session administered in order to familiarize them with the experimental task.

The experimental task is illustrated in Fig. 1. It was divided into six blocks of 15 trials (five consecutive trials per condition). Each trial started with the presentation of a central fixation cross (1 s), followed by a target display of items (3 s). This period was defined as the encoding phase. The target display consisted of three words and three spatial locations defined by an ellipse. The words were selected from the French Lexicon Project (Ferrand et al., 2010). Within a target display, the three words were semantically unrelated. Five naive raters validated the absence of semantic links between the three words of each target display.

The presentation of verbal and spatial information differed depending on the experimental condition. In the "active binding" condition, the three words were central, and separated from the three ellipses. In this condition, participants had to mentally link the verbal and spatial information sharing the same color (e.g. the word in red must be associated with the position defined by a red ellipse). In the "passive binding" condition, words were already included within ellipses. Binding here was deemed "passive", as verbal and spatial information was presented as already integrated. Then, a probe composed of a word and a spatial location was presented (3 s). This period was defined as the retrieval phase. In both binding conditions, a word within an ellipse was presented. Participants had to decide whether their pairing was identical to the encoding phase or not (i.e., the word was associated with a location that was previously paired with another word). Thus, making correct responses in spite of re-pairings presented as distractors required accurate memory not only for verbal and spatial information, but also for their pairing (Mitchell et al., 2000). After a blank screen of 10 s, a new trial began. This long inter-trial interval was used to avoid elevated baseline activity prior to the onset of the next display (Yamasaki et al., 2002). A third condition, in which memory for isolated letters and spatial locations was assessed, was also included. However, this condition was not presented here, considering that the paper focuses on the differences between active and passive binding. Exclusion of this condition does not influence the conclusion of the manuscript.

2.3. FMRI scanning protocol

The scanning sessions were carried out at the Institut Universitaire de Gériatrie de Montréal (IUGM) on a 3 T scanner (Siemens Magneton TRIO). The scanning sessions began with the acquisition of functional images over the entire brain using a T2* BOLD EPI sequence along the AC-PC axis (TR = 2.25 s/TE = 30 ms/Flip angle = 90°/37slices/resolution = $3 \times 3 \times 3$ mm^3). The first three scans were removed to obtain a steady-state T1 partial saturation effect. Finally, an anatomical MRI using a 3D T1-weighted (TR = 22 ms/TE = 9.2 ms/flip angle = 30°/FOV = 256 mm/176 slices/resolution = $1 \times 1 \times 1$ mm^3) was performed.

[1] SZ is usually associated with intellectual deficits, as reflected by a lower IQ score in patients relative to controls. However, patients' IQ score did not differ significantly from mean 100 ($t_{18} = --1.29$; $p = 0.21$). In addition, the parental socio-economic status was used as a measure of premorbid functioning.