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 these dysfunctions may be targets for neuromodulation interventions known to improve cognitive deficits in schizophrenia.

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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 evaluated with the WAIS-III.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with SZ</th>
<th>Controls</th>
<th>Analysis (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 19</td>
<td>N = 23</td>
<td></td>
</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.30</td>
<td>32.78</td>
<td>0.20</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/5</td>
<td>15/8</td>
<td>0.55</td>
</tr>
<tr>
<td>Handednessc</td>
<td>0.84</td>
<td>0.78</td>
<td>0.63</td>
</tr>
<tr>
<td>Parental SES scoreb</td>
<td>51.88</td>
<td>45.83</td>
<td>0.28</td>
</tr>
<tr>
<td>IQc</td>
<td>96.21</td>
<td>105.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic dosea</td>
<td>349.76</td>
<td>(47.26)</td>
<td></td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>16.16</td>
<td>(1.18)</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>15.89</td>
<td>(0.90)</td>
<td></td>
</tr>
<tr>
<td>PANSS General</td>
<td>34.38</td>
<td>(2.04)</td>
<td></td>
</tr>
</tbody>
</table>

a Edinburgh Handedness Inventory.

b Hollingshead Parental Socio-Economic Status.

c Evaluated with the WAS-III.

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.

2.2. 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.

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

2.4.1. Behavioral analyses

Behavioral performance was analyzed using Statistica 6.0 (Statsoft). Accuracy was estimated using the Pr index (Hits – False Alarms), to provide an objective measure of sensitivity that is independent of participant response bias (Snodgrass and Corwin, 1988). A repeated-measure analysis of variance (ANOVA) was performed with the group (patients vs. controls) entered as between-group factor and binding conditions (passive binding vs. active binding) as within-group factor. When needed, Duncan test comparisons were performed for post-hoc analyses. In all behavioral analyses, the alpha level was set at 0.05.

2.4.2. Neuroimaging analyses

Analyses were performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/spm8). First, for preprocessing, functional images were realigned to the first volume in their respective run, and then normalized to the Montreal Neurological Institute (MNI) template. Then, data were spatially smoothed using a 3D 8-mm Gaussian filter. High-pass and low-pass filters were applied to filter out physiological artifacts. Prior to individual analyses, the movement correction logs were examined to ensure that none of the participants presented movements >5 mm or 5°. In addition, head translation and head rotation were extracted during the preprocessing realignment and included as covariates in the first-level models. Four event types were modeled in each binding condition: encoding, early period of maintenance, late period of maintenance, and retrieval. The maintenance phase was split into two separate regressors, as different processes are associated with the early and the late maintenance (Naveh-Benjamin and Jonides, 1984). The cut off was set at 3 s in accordance with previous studies (Bergmann et al., 2013; Khader et al., 2007). For each of the four phases, an individual [active – passive] contrast was generated. These individual activation maps were then pooled into a second-level analysis to perform a random-effect group analysis (two-sample t-test) for each group (Friston et al., 2002). To address the issue of multiple comparisons, a cluster-extent based correction, determined through Monte-Carlo simulation, with the Matlab script developed by Slotnick et al. (2003). Results of our simulation indicated that, given a voxel-wise intensity threshold of \( p < 0.005 \) and the whole-brain search space, a cluster extent threshold of 51 contiguous voxels would be necessary to achieve an overall type I error rate of \( p < 0.05 \), corrected for multiple comparisons. This combination of intensity and extent thresholds has been deemed appropriate in yielding a good balance between Type I and II error rates (Lieberman and Cunningham, 2009).

2.4.3. Additional analyses

Pearson correlations were also performed to examine the potential impact of medication and symptoms on both behavioral performance and BOLD signals. \( B-Y \) method FDR corrections were applied to control for multiple comparisons (Narum, 2006).

3. Results

3.1. Behavioral results

Pr scores are illustrated in Fig. 2, and summarized in Table 2. The group X binding conditions ANOVA showed a significant effect of group (\( F(1,40) = 6.56; p = 0.02 \)) with patients’ overall performance being lower than that of controls. There was also a significant effect of conditions (\( F(1,40) = 23.27; p < 0.001 \)), with greater performance in the passive than active binding task. Finally there was a significant group X conditions interaction (\( F(1,40) = 4.56; p = 0.04 \)). Post-hoc analyses revealed that patients exhibited significantly lower performance for active binding relative to controls (\( p < 0.02 \)), but performed equally well as controls for passive binding (\( p = 0.31 \)).

3.2. FMRI results

For concision purpose, only between-group differences are presented in the following sections; intra-group activations are reported in the Supplementary material.
3.2.1. Encoding

Between-group contrasts showed greater activation in controls relative to patients with SZ in the superior and inferior parietal lobules bilaterally, the lingual gyrus bilaterally, the left fusiform gyrus, the precentral gyrus bilaterally, the left superior frontal gyrus, the right postcentral gyrus and the right cerebellum (Fig. 3 and Table S1). In contrast, patients exhibited no greater activation than controls.

3.2.2. Early maintenance

Analyses revealed that controls showed greater activations than patients in the left ventrolateral prefrontal cortex (VLPFC) (Fig. 4 and Table S2). Conversely, patients with SZ exhibited greater activation than controls in the left thalamus, and the left postcentral gyrus.

3.2.3. Late maintenance

Between-group differences showed greater activations in controls relative to patients in the left inferior parietal lobule and the left precenral gyrus. In contrast, patients exhibited no greater activations than controls (Table S3).

3.2.4. Retrieval

Finally, patients with SZ showed a lower activation in the left cerebellum and left fusiform gyrus relative to controls. Conversely, patients exhibited no greater activations than controls (Table S4).

4. Discussion

4.1. A specific deficit of active binding in SZ

This FMRI study aimed to investigate the neural basis of active and passive binding in WM in SZ. At the behavioral level, our study revealed that patients with SZ were able to correctly memorize already bound information. Such results are in line with our previous works on passive binding in WM (Luck et al., 2008, 2009, 2010), and with our meta-analysis conclusions (Grot et al., 2014). The novelty is that patients exhibited a specific deficit in voluntarily binding information. This deficit may not result from a reduced memory span (Barch and Ceaser, 2012), or difficulties to simultaneously process different types of information, since both experimental conditions were composed of the same amount of information (i.e. three letters and three spatial positions), and the patients exhibited similar performance to that of controls for the passive binding condition. Instead, the specific deficit of active binding in patients with SZ can be explained by three not mutually exclusive hypotheses linked to the differences identified in brain activity, as discussed below.

4.2. Evidence for abnormal posterior parietal cortex and VLPFC functioning in SZ

1. Does posterior parietal activity reflect patients’ attentional difficulties? It has been suggested that maintaining bound information in WM requires additional attentional resources than maintaining discrete information (Allen et al., 2006; Wheeler and Treisman, 2002), and this especially for active/intentionally bound information (Morey, 2011). Active processes require additional attentional resources. Specifically, during encoding, active binding requires focusing and switching attention to all the displayed information (Corbetta et al., 1995), involving inferior (Nee et al., 2013; Nee and Jonides, 2008) and superior parietal cortex activity (Chiu and Yantis, 2009; Wager et al., 2004; Wang et al., 2015), respectively. Thus, the deficit for active binding observed in patients may result from their inability to switch and maintain focused attention on the link between verbal and spatial information. However, this attention-deficit hypothesis hardly explains the deficit specificity for active binding, since other studies have found contradictory results suggesting that maintaining bound information in WM does not require more attentional resources than maintaining discrete information (Allen et al., 2006; Vogel et al., 2001). Consequently, lower performance in patients relative to controls should have been observed in both binding conditions. Additionally, the observed posterior parietal cortex

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Table 2
Mean and SEM proportions of Pr index (hits, H – false alarms, FA), as a function of experimental conditions for patients with schizophrenia (SZ) and controls.

<table>
<thead>
<tr>
<th></th>
<th>Passive binding</th>
<th>Active binding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>FA</td>
<td>Pr</td>
</tr>
<tr>
<td>H</td>
<td>0.81</td>
<td>0.08</td>
<td>0.74</td>
</tr>
<tr>
<td>(0.02)</td>
<td>(0.06)</td>
<td>(0.04)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Patients with SZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.85</td>
<td>0.02</td>
<td>0.83</td>
</tr>
<tr>
<td>(0.01)</td>
<td>(0.01)</td>
<td>(0.04)</td>
<td>(0.03)</td>
</tr>
<tr>
<td></td>
<td>0.74</td>
<td>0.23</td>
<td>0.51</td>
</tr>
<tr>
<td>(0.03)</td>
<td>(0.05)</td>
<td>(0.08)</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>0.85</td>
<td>0.10</td>
<td>0.75</td>
</tr>
<tr>
<td>(0.03)</td>
<td>(0.02)</td>
<td>(0.06)</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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hypoactivation during encoding would have been observed during both early and late maintenance as well. To sum up, the explanation that the active binding deficit may result from limited attentional resources is only partially supported by our results.

2. Does posterior parietal activity reflect patients’ failure to manipulate information? Another hypothesis relies on a deficit of information manipulation. Unlike the passive binding condition, the active binding condition required the manipulation of verbal and spatial information to voluntarily and consciously create a link between them. Behavioral studies in WM have shown that patients with SZ have marked difficulties in manipulating information in WM (Barch, 2005; Park and Gooding, 2014), to a greater extent than for its encoding and maintenance. This hypothesis is strengthened by our results of hypoactivation of the posterior parietal cortex during encoding, a cerebral region involved in the manipulation of information in WM (Champod and Petrides, 2007; Koenigs et al., 2009; Owen et al., 2005). Such a hypoactivation may indicate that patients, unlike controls, failed to manipulate or reorganize verbal and spatial information efficiently during their initial presentation, and were thereby unable to create unified representations.

Fig. 3. FMRI results for the encoding. Section A illustrates between-group comparisons during the encoding period. Greater activations in controls relative to patients with SZ are showed in warm colors. Section B illustrates beta values in the left SPL, and IPL bilaterally in controls and in patients with SZ. PG, Postcentral Gyrus; PCG, Precentral Gyrus; IPL, Inferior Parietal Lobule; SPL, Superior Parietal Lobule; IOG, Inferior Occipital Gyrus; LG, Lingual Gyrus; FG, Fusiform Gyrus.

Fig. 4. FMRI results for the early maintenance. Section A illustrates between-group comparisons during the early maintenance period. Greater activations in controls relative to patients with SZ are showed in warm colors, whereas greater activations in SZ patients relative to controls are showed in cold colors. Section B illustrates beta values in the left VLPFC. VLPFC, Ventro-Lateral Prefrontal Cortex; PG, Postcentral Gyrus; Th, Thalamus.

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3. Does VLPFC mediates binding or encoding strategies failure in patients? Beside increased activity in the posterior parietal cortex during early maintenance, patients also exhibited reduced activity in the VLPFC. This region is considered to be involved in articulatory rehearsal, which is essential for maintaining discrete verbal information (Gruber et al., 2006; Rottschy et al., 2012), as well as bound verbal and spatial information (Campos et al., 2010). Thus, hypoactivation of the VLPFC may reflect the patients’ difficulties to maintain integrated representations in WM, as they did not create such representations during encoding. Another explanation is that patients, unlike controls, did not use effective strategies to maintain bound information in our task. As pinpointed by Bor et al. (2003), the VLPFC is involved in the generation of cognitive strategies to maintain complex information in memory. Thus, lower VLPFC activity in patients may reflect their inability to spontaneously use efficient strategies to maintain information in WM (Bonner-Jackson and Barch, 2011; Bonner-Jackson et al., 2005), leading to poorer performance for the active binding condition.

4.3. Caveats

The effect of psychotropic drugs may constitute a limitation to this study. As all patients were taking antipsychotic medication during our study, their effect cannot be ruled out completely, and the possibility that this may have had an influence on our results cannot be discounted. However, there was no significant correlation between behavioral performance or BOLD signal and the mean dose of antipsychotic medication. This suggests that the dose of the medication did not have a significant impact on the results. Another limitation is that we did not strictly control for literacy, which is associated with poor cognitive functioning in patients (Clegg et al., 2005; Dickson et al., 2014). Although all participants reported having completed their high school training, ensuring a minimum level of literacy, we consider that further investigations are required to examine more in detail the impact of literacy on active binding deficits in patients with SZ.

5. Conclusion

Our study disentangled preserved from altered processes of WM in SZ, arguing against a generalized deficit. More precisely, our results showed that patients with SZ may suffer from a lack of attention, manipulation, and the use of strategies which are required for correctly memorizing actively bound information in WM. This results from the abnormal functioning of the posterior parietal cortex and the VLPFC. Such a dysfunction may constitute the target for new therapeutic interventions, such as neuromodulation techniques, known to improve different aspects of cognition (Brunoni and Vanderhasselt, 2014; Demirtas-Tatlidede et al., 2013; Lett et al., 2014).

Role of the funding source

This study was supported by the Brain and Behavior Research Foundation (#18917) and the Quebec Bioimaging Network (#5.06). Dr. Luck is supported by a salary award from the Fonds de recherche en santé du Québec (FRSQ) (#27178). Dr. Dolcos was supported by a Helen Corley Petit Endowed Scholarship and an Emanuel Donchin Professorial Scholarship from the University of Illinois.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Author SG acquired and analyzed the data, interpreted results, and wrote the first draft of the manuscript. Author VPL, and FD collaborated in the writing of the final version of the manuscript. Authors OL and IS supervised clinical and neuropsychological assessments. Author DL conceptualized the study, supervised the study, provided laboratory space and resources for data analyses. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.01.021.

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