Altered engagement of attention and default networks during target detection in schizophrenia

Wendy Hasenkamp,⁎ G. Andrew James, William Boshoven, Erica Duncan

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A B S T R A C T
Recent studies have implicated inappropriate engagement of functional brain networks in schizophrenia. This fMRI study examined task-induced activations and deactivations in 10 schizophrenia patients with prominent negative symptoms and 10 healthy controls during a simple target detection task. Group comparison revealed recruitment of distinct attentional networks during this task, with schizophrenia subjects activating the dorsal attention system and controls activating the executive network. Further, schizophrenia patients failed to deactivate posterior cingulate regions during the task, supporting recent studies of altered default mode processing. These findings support theories of dysfunctional recruitment of large-scale brain networks in schizophrenia.

1. Introduction

The default mode network (DMN) is an interrelated group of brain regions that is preferentially activated during undirected rest periods, and deactivated during cognitive tasks requiring engaged attention on the external environment (Buckner et al., 2008; Gusnard et al., 2001; Raichle et al., 2001). The DMN is made up of posterior cingulate cortex (PCC), medial prefrontal cortex (PFC), inferior parietal lobule, lateral temporal cortex, and hippocampal formation including parahippocampus (Buckner et al., 2008). Recent evidence suggests that schizophrenia may be associated with a reduction in normal task-induced deactivation (TID) within the DMN, based on findings that activity in key DMN regions persists inappropriately into task periods (Kim et al., 2009; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009).

In addition to the DMN, another large distributed brain network has recently been characterized. This task-positive network is generally activated during tasks involving focused attention and goal-directed behavior (Corbetta et al., 2008; Corbetta and Shulman, 2002), and is deactivated at rest, thereby showing an anticorrelated pattern of activation from the DMN (Fox et al., 2005; Fransson, 2005). The task-positive network is made up of lateral PFC, sensory and motor cortices, inferior parietal lobules, occipital regions, insula and anterior cingulate cortex (Fox et al., 2005; Fransson, 2005). Numerous subdivisions within the larger task-positive attention network have been proposed in light of task-based and functional connectivity studies; two major subnetworks are the dorsal attention and executive systems. The dorsal attention network includes precentral regions/frontal eye fields and intraparietal sulcus, and functions to prepare and apply top-down goal-directed selection in tasks such as visual target detection (Corbetta et al., 2008; Corbetta and Shulman, 2002). Conversely, the frontoparietal executive network consists of the dorsolateral PFC and posterolateral parietal cortex, and is activated during tasks requiring sustained...
attention, working memory and decision making (Curtis and D’Esposito, 2003; Seeley et al., 2007). Schizophrenia has been repeatedly associated with executive dysfunction, and neuroimaging studies show reduced task-induced activation (TIA) of dorsolateral PFC (Forbes et al., 2009; Minzenberg et al., 2009).

We conducted an fMRI study to explore TIA and TID in schizophrenia patients with prominent negative symptoms using a simple target detection task. A between-group comparison with healthy controls was performed, as well as investigation of activation patterns within each group separately. Results confirmed reduced TID in schizophrenia, and also revealed very different patterns of TIA between groups. These findings implicate alterations in intrinsic brain networks in schizophrenia, including dorsal attention and executive networks, and the DMN.

2. Materials and methods

2.1. Subjects

Twelve right-handed adult male schizophrenia (SCZ) patients with prominent negative symptoms and 12 right-handed healthy male controls (CON) were recruited and signed a consent form approved by the Institutional Review Board at Emory University and the Atlanta VA Research and Development Committee. The diagnosis of schizophrenia was established on the basis of chart review and the Structured Clinical Interview for DSM-IV, Axis-I (SCID-I: First et al., 2001), and symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The SCID-I was also administered to CON subjects in order to rule out Axis-I disorders. Exclusion criteria were: current substance dependence, positive urine toxicology, history of sustained loss of consciousness, major neurological or medical illness, left-handedness, or history of Axis-I mental illness (CON subjects only). All patients were stabilized on medication. Data from two SCZ and two CON subjects were excluded due to excessive head motion; thus, the final sample size was 10 SCZ and 10 CON subjects. Demographic, clinical and behavioral data are listed in Table 1.

2.2. Cognitive task

Subjects underwent fMRI scanning while performing a simple visual target detection task (modified from Elliott et al., 2003), described in more detail in Supplementary methods. Briefly, subjects were instructed to press a button when they saw a green or blue square (targets), which were presented randomly and interspersed with squares of other colors (non-targets). Sixteen blocks of 22 trials each (36% targets) were presented over the course of 20 min, separated by 30-second rest periods (fixation).

2.3. fMRI data analysis

Functional MRI data was analyzed in AFNI (Cox, 1996); imaging parameters and preprocessing steps are provided in Supplementary methods. For the present analysis, all trials were collapsed and analyzed as a simple block design to investigate BOLD responses during the overall “task vs. rest” comparison. For each subject, betas at each voxel (whole brain) were estimated from percent signal change data using a general linear model, which also included: 1) a basis set of 9th order polynomial functions, modeling low-frequency confounds; 2) the subject’s motion parameters, treated as confounds; and 3) one regressor function modeling the task, constructed by convolving box-car functions of the time frames corresponding to task blocks with a canonical gamma hemodynamic response function. Each subject’s betas for the task vs. rest contrast were then entered into a two-way ANOVA, with group as the between-subjects factor and subject as a random effect. In addition to computing the group contrast, group means were also extracted for the purposes of investigating each group individually. A voxelwise significance level of p<0.005 was used to threshold the resulting activation maps (whole brain threshold of p<0.05 corrected for multiple comparisons). A spatial extent threshold of 20 functional voxels was established using AlphaSim in AFNI, which runs Monte Carlo simulations to correct for multiple comparisons by estimating extent thresholds needed to exceed cluster sizes of false positives at a given voxelwise threshold.

3. Results and discussion

3.1. Task-induced deactivations

CON subjects showed a widespread bilateral region of TID in the PCC and surrounding areas, as well as the right posterior insula (Table 2, Fig. 1A). In SCZ patients, TID was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical information by group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCZ (n=10)</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>42.5±10.9</td>
</tr>
<tr>
<td>Education (years, mean±SD)</td>
<td>12.8±1.7</td>
</tr>
<tr>
<td>IQ (mean±SD)</td>
<td>91.6±10.7</td>
</tr>
<tr>
<td>Race (frequency)</td>
<td>7</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Smoker (frequency)</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Task variables</td>
<td>96.9±43.5</td>
</tr>
<tr>
<td>Performance (% hits, mean±SD)</td>
<td>55.1±48.7</td>
</tr>
<tr>
<td>Medication (frequency)</td>
<td>15.2±5.3</td>
</tr>
<tr>
<td>Atypicals</td>
<td>1</td>
</tr>
<tr>
<td>Typical</td>
<td>–</td>
</tr>
<tr>
<td>No antipsychotic</td>
<td>–</td>
</tr>
<tr>
<td>PANSS rating (mean±SD)</td>
<td>23.0±7.5</td>
</tr>
<tr>
<td>Total</td>
<td>69.4±17.2</td>
</tr>
</tbody>
</table>

a Age between groups: p=0.36.
b Education between groups: p=0.01.
c IQ between groups: p=0.02.
d Race between groups: p=0.27.
e Smoking between groups: p=0.36.
f Performance between groups: p=0.26.
g Response time between groups: p=0.27.
limited to a small region in the right PCC/precuneus, overlapping with only 9.6% of TID seen in the CON subjects (green in Fig. 1A). Thus, these negative-symptom SCZ subjects showed a large reduction in TID within the central hub of the DMN (Buckner et al., 2008). Many studies have shown dysregulation of DMN in schizophrenia, although the precise manner of disease-related alterations is still unclear (Broyd et al., 2009; Mannell et al., 2010). The present results are consistent with a growing body of evidence that suggests a hyperactive DMN in schizophrenia, whereby activity in regions of the DMN persists inappropriately into task periods (Kim et al., 2009; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). This failure to deactivate the DMN has been found previously in working memory tasks, and this study extends this pattern to tasks involving low-cognitive load target detection.

### 3.2. Task-induced activations

Comparison of activations during the task revealed a striking difference in the patterns of activity between SCZ and CON groups (Table 2, Fig. 1B). TIA in CON subjects was mainly in frontoparietal attention regions, including dorsolateral PFC and inferior parietal cortex. These regions are consistent with the executive network, which exerts control over posterior sensorimotor representations and maintains relevant information via working memory until a response is selected (Corbetta et al., 2008; Curtis and Lee, 2010; Seeley et al., 2007). In contrast, activations in SCZ patients were mainly localized to sensory, motor, visual and insular cortex. These regions are all included in the dorsal attention system (Corbetta et al., 2008), which is thought to prepare and apply top-down goal-directed orienting or selection. Overall, there was only a 5.4% overlap between the two groups’ activation maps (green in Fig. 1B).

Results from the whole brain between-group comparison identified five clusters that were significantly more active in SCZ than CON subjects (Table 2), which also span bilateral dorsal attention network regions, including premotor and supplementary motor areas, primary motor and somatosensory regions, insula and inferior parietal lobule.

Taken together, these findings suggest that BOLD responses during simple target detection in SCZ patients may involve dysregulation of multiple subnetworks within the task-positive attention network, specifically hyperactivation of the dorsal attention system and hypoactivation of the executive network. Schizophrenia has long been associated with dysfunctional executive systems, particularly with regard to hypoactivation or inappropriate recruitment of the dorsolateral PFC (Forbes et al., 2009; Menzenberg et al., 2009), which agrees with the current findings. In addition, several studies have reported hyperactivation of sensorimotor regions during target detection in oddball tasks in schizophrenia (Gur et al., 2007; Huang et al., 2010; Wolf et al., 2008), although the dorsal attention system, per se, has not been previously implicated in the disease. It is possible that in the face of reduced functionality of executive regions, SCZ patients may require additional top-down orienting, provided by the dorsal attention system (Corbetta et al., 2008), to maintain focus on the task. Further, as no differences were seen in performance or reaction time (Table 1), SCZ subjects may engage elements of the dorsal attention system regions, including premotor and somatosensory regions, insula and inferior parietal lobule.

### 3.3. Overall conclusions

The results of this analysis show that during simple target detection, SCZ patients with prominent negative symptoms
show altered activity in several intrinsic neural networks, including DMN, dorsal attention and executive networks. These findings add to growing evidence for improper recruitment of functional brain networks during attentional tasks, and support suggestions of aberrant connectivity between task-positive and task-negative networks in schizophrenia. Further characterization of these networks with task-based and functional connectivity studies is warranted to increase our understanding of the neural basis of schizophrenia.

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Contributors
Author Hasenkamp managed the statistical analysis, literature search and the writing/editing of the manuscript.
Author James aided in statistical analysis.
Author Boshoven collected data from subjects and managed data entry.
Author Duncan designed the study, wrote the protocol, obtained grant funding, directed data collection, helped collect data and edited the manuscript.
All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors declare that they have no conflicts of interest regarding this manuscript.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at doi:10.1016/j.schres.2010.08.041.

References