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

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ABSTRACT

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.

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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

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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.

Table 1
Demographic and clinical information by group.

	SCZ ($n=10$)	CON ($n=10$)
Age (years, mean ± SD) [a]	42.5 ± 10.9	38.6 ± 7.2
Education (years, mean ± SD) [b]	12.8 ± 1.7	16.5 ± 3.6
IQ (mean ± SD) [c]	91.6 ± 10.7	109.0 ± 17.5
Race (frequency) [d]		
African American	7	5
Caucasian	2	5
Other	1	0
Smoker (frequency) [e]		
Yes	6	1
No	4	9
Task variables		
Performance (% hits, mean ± SD) [f]	96.9 ± 43.5	99.2 ± 0.3
Response time (ms, mean ± SD) [g]	55.1 ± 48.7	51.4 ± 57.3
Medication (frequency)		
Atypicals	9	–
Typicals	1	–
Atypical + typical	–	–
No antipsychotic	–	–
PANSS rating (mean ± SD)		
Positive symptoms	15.2 ± 5.3	–
Negative symptoms	23.0 ± 7.5	–
General psychopathology	31.2 ± 7.4	–
Total	69.4 ± 17.2	–

[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: $p=0.02$.
[f] Performance between groups: $p=0.26$.
[g] Response time between groups: $p=0.27$.

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 voxel-wise 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 voxel-wise 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