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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

Table 2
Activations, deactivations and group differences during task.

	Brodmann area	Voxels	Peak			Mean *t*-value
			x	y	z	
CON only						
Activations						
R IFG	9	57	45	1	36	5.05
R IPL	40	27	48	-31	48	4.77
L IPL/SPL	7	53	-34	-55	48	4.66
L IPL	40	54	-48	-37	45	4.48
R MFG	9	20	52	25	30	4.45
L MFG/IFG	9	60	-41	4	39	4.44
R cuneus	17/18	28	14	-92	15	4.18
Deactivations						
PCC/precuneus/cuneus	30,31,17,18	544	7	-65	24	-4.80
R STG/posterior insula	22,13	34	52	-6	3	-4.14
SCZ only						
Activations						
R precentral gyrus/PMC	4,6	76	38	-10	51	5.12
Medial frontal gyrus/SMA	6,24	196	-3	-3	57	4.87
L pre/postcentral gyrus/PMC	2,3,4,6	570	-38	-31	57	4.80
L MTG	37	57	-48	-65	6	4.63
R MTG	37	74	45	-65	9	4.59
L IPL	40	46	-55	-41	27	4.56
L middle insula	13	76	-48	1	9	4.52
R cuneus	18,19	32	21	-86	21	4.45
R middle insula	13	27	45	1	12	4.40
L cuneus	18	35	-17	-99	18	4.29
R PHG	37	19	28	-44	-7	4.16
R thalamus/caudate	–	24	7	-3	12	4.07
Deactivations						
R PCC/precuneus/cuneus	30,31,18	81	10	-75	21	-4.42
Group differences (SCZ>CON)						
L IPL/posterior insula	40,13	23	-52	-37	21	4.81
R middle insula/precentral gyrus	13,44	24	48	1	12	4.61
R medial frontal gyrus/SMA	6	38	7	-6	51	4.53
R pre/postcentral gyrus	4,1	34	38	-27	63	4.50
L precentral gyrus/PMC	4,6	122	-24	-20	57	4.47

Significant clusters for task-induced activations and deactivations ($p<0.005$, 20 functional voxels, corrected for multiple comparisons over the whole brain to $p<0.05$ using AFNI AlphaSim). R: right; L: left; if R or L not listed, clusters are bilateral. IFG: inferior frontal gyrus, IPL: inferior parietal lobule, MFG: middle frontal gyrus, MTG: middle temporal gyrus, PCC: posterior cingulate cortex, PHG: parahippocampal gyrus, PMC: premotor cortex, SMA: supplementary motor area, SPL: superior parietal lobule, STG: superior temporal gyrus.

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; Minzenberg 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 network as a compensatory strategy. Alternatively, these hyperactivations may represent a failure to properly deactivate these regions, as has been shown in other networks (Kim et al., 2009; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009).

3.3. Overall conclusions

The results of this analysis show that during simple target detection, SCZ patients with prominent negative symptoms

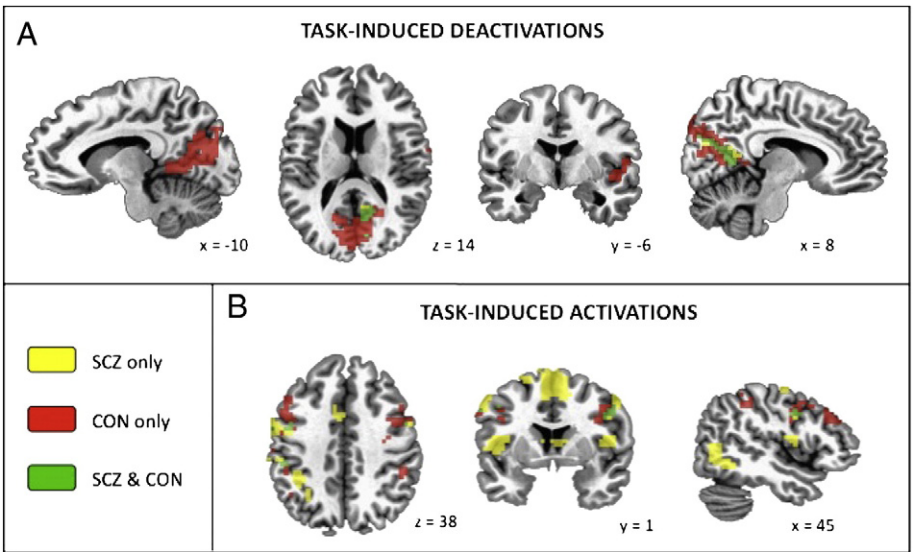

Fig. 1. Average task-induced deactivations (A) and activations (B) within SCZ and CON subjects; whole brain voxel-wise analysis, significant at $p<0.005$, 20 functional voxels, corrected for multiple comparisons over the whole brain to $p<0.05$ using AFNI. Within each panel, voxels specific to SCZ subjects are shown in yellow, while voxels specific to CON subjects are shown in red. Green voxels represent an overlap between SCZ and CON. (A) CON subjects show a broad bilateral area of task-induced deactivation (TID) centered in the PCC. SCZ subjects show a much smaller region of TID in the right PCC, overlapping only 9.6% of that of CON. (B) During the target detection task, CON subjects activated frontoparietal executive regions. In contrast, SCZ subjects activated many elements of the dorsal attention system, and failed to activate the executive system. The overlap between CON and SCZ activations is only 5.4% of the total voxels, implying markedly different patterns of brain activity between groups.

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

Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J., 2009. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci. Biobehav. Rev. 33 (3), 279–296.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124, 1–38.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3 (3), 201–215.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58 (3), 306–324.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29 (3), 162–173.

Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cogn. Sci. 7 (9), 415–423.

Curtis, C.E., Lee, D., 2010. Beyond working memory: the role of persistent activity in decision making. Trends Cogn. Sci. 14 (5), 216–222.

Elliott, R., Newman, J.L., Longe, O.A., Deakin, J.F., 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. J. Neurosci. 23 (1), 303–307.

First, M., Spitzer, R.L., Gibbon, M., Williams, J., 2001. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. Biometrics Research Department: New York State Psychiatric Institute.

Forbes, N.F., Carrick, L.A., McIntosh, A.M., Lawrie, S.M., 2009. Working memory in schizophrenia: a meta-analysis. Psychol. Med. 39 (6), 889–905.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl Acad. Sci. USA 102 (27), 9673–9678.

Fransson, P., 2005. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum. Brain Mapp. 26 (1), 15–29.

Gur, R.E., Turetsky, B.I., Loughead, J., Snyder, W., Kohler, C., Elliott, M., Pratiwadi, R., Ragland, J.D., Bilker, W.B., Siegel, S.J., Kanes, S.J., Arnold, S.E., Gur, R.C., 2007. Visual attention circuitry in schizophrenia investigated with oddball event-related functional magnetic resonance imaging. Am. J. Psychiatry 164 (3), 442–449.

Gusnard, D.A., Raichle, M.E., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nat. Rev. Neurosci. 2 (10), 685–694.

Huang, M.X., Lee, R.R., Gaa, K.M., Song, T., Harrington, D.L., Loh, C., Theilmann, R.J., Edgar, J.C., Miller, G.A., Canive, J.M., Granholm, E., 2010. Somatosensory system deficits in schizophrenia revealed by MEG during a median-nerve oddball task. Brain Topogr. 23 (1), 82–104.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kim, D.I., Manoach, D.S., Mathalon, D.H., Turner, J.A., Mannell, M., Brown, G.G., Ford, J.M., Gollub, R.L., White, T., Wible, C., Belger, A., Bockholt, H.J., Clark, V.P., Lauriello, J., O'Leary, D., Mueller, B.A., Lim, K.O., Andreasen, N., Potkin, S.G., Calhoun, V.D., 2009. Dysregulation of working memory and default-mode networks in schizophrenia using independent component analysis, an fBIRN and MCIC study. Hum. Brain Mapp. 30 (11), 3795–3811.

Mannell, M.V., Franco, A.R., Calhoun, V.D., Canive, J.M., Thoma, R.J., Mayer, A.R., 2010. Resting state and task-induced deactivation: a methodological comparison in patients with schizophrenia and healthy controls. Hum. Brain Mapp. 31 (3), 424–437.

Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch. Gen. Psychiatry 66 (8), 811–822.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., Cebamanos, J.M., McKenna, P.J., 2008. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychol. Med. 38 (8), 1185–1193.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl Acad. Sci. USA 98 (2), 676–682.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27 (9), 2349–2356.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D.E., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl Acad. Sci. USA 106 (4), 1279–1284.

Wolf, D.H., Turetsky, B.I., Loughead, J., Elliott, M.A., Pratiwadi, R., Gur, R.E., Gur, R.C., 2008. Auditory oddball fMRI in schizophrenia: association of negative symptoms with regional hypoactivation to novel distractors. Brain Imag. Behav. 2 (2), 132–145.