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Multimodal analyses identify linked functional and white matter abnormalities within the working memory network in schizophrenia

Gisela Sugranyes^{1,2,3}, Marinos Kyriakopoulos^{1,2}, Danai Dima¹, Jonathan O'Muirheartaigh⁴, Richard Corrigan², Gabrielle Pendelbury¹, Daniel Hayes², Vince D. Calhoun^{5,6,7}, and Sophia Frangou¹

¹Section of Neurobiology of Psychosis, Dept. of Psychosis Studies, Institute of Psychiatry, King's College London, UK

²Child and Adolescent Mental Health Services, South London and Maudsley NHS Foundation Trust, UK

³Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic of Barcelona, Spain

⁴Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, UK

⁵The Mind Research Network, Albuquerque, NM, USA

⁶Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, USA

⁷Dept. of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Abstract

Background—Dysconnectivity between brain regions is thought to underlie the cognitive abnormalities that characterise schizophrenia (SZ). Consistent with this notion functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) studies in SZ have reliably provided evidence of abnormalities in functional integration and in white matter connectivity. Yet little is known about how alterations at the functional level related to abnormalities in anatomical connectivity.

Methods—We obtained fMRI data during the 2-back working memory task from 25 patients with SZ and 19 healthy controls matched for age, sex and IQ. DTI data were also acquired in the

Corresponding author: Sophia Frangou, Section of Neurobiology of Psychosis, Institute of Psychiatry, King's College London, De Crespigny Park, London, SE5 8AF, UK, Tel: +442078480425; Fax: +442078480983; sophia.frangou@kcl.ac.uk.

Conflict of interest

There are no conflicts of interest to report for any of the authors.

Contributors

GS managed the literature review, conducted neuroimaging analyses, and wrote the first draft of the manuscript. DM and JOM conducted neuroimaging analyses and assisted with data interpretation and editing of the manuscript. Authors MK, RC, DP and DH oversaw the recruitment and clinical assessment of the sample, aided in study design and in editing the manuscript. VC directed the neuroimaging data analyses, interpretation of the results and assisted in writing the manuscript. SF designed the study, directed data collection, analysis and interpretation of results, and edited the manuscript. All authors contributed to and have approved the final manuscript.

same session. In addition to conventional unimodal analyses we extracted “features” [contrast maps for fMRI and fractional anisotropy (FA) for DTI] that were subjected to joint independent component analysis (JICA) in order to examine interactions between fMRI and DTI data sources.

Results—Conventional unimodal analyses revealed both functional and structural deficits in patients with SZ. The JICA identified regions of joint, multimodal brain sources that differed in patients and controls. The fMRI source implicated regions within the anterior cingulate and ventrolateral prefrontal cortex and in the cuneus where patients showed relative hypoactivation and within the frontopolar cortex where patients showed relative hyperactivation. The DTI source localised reduced FA in patients in the splenium and posterior cingulum.

Conclusions—This study promotes our understanding of structure-function relationships in SZ by characterising linked functional and white matter changes that contribute to working memory dysfunction in this disorder.

Keywords

fmri; diffusion tensor imaging; independent component analysis; early onset schizophrenia

1. Introduction

Working memory disruption is considered a core cognitive dimension of schizophrenia (SZ) (Goldman-Rakic 1994). Functional magnetic resonance imaging (fMRI) studies consistently link working memory impairment in SZ with inefficient engagement of the dorsolateral prefrontal cortex (DLPFC) coupled with increased activity in the anterior cingulate cortex (ACC) and in frontopolar regions (Glahn et al 2005). These observations are considered indicative of reduced functional integration within the working memory network (Gruber et al., 2006; Kim et al., 2009; Meda et al., 2009; Meyer-Lindenberg and Weinberger, 2006; Schlösser et al., 2003; White et al., 2011) and have been attributed to abnormal anatomical connectivity within the DLPFC (Selemon et al., 1995; Uranova et al., 2007) and between the DLPFC and posterior brain regions (Ellison-Wright and Bullmore, 2009). Anatomical connectivity in SZ, as inferred through measures of the directional organisation of white matter tracts, has been examined using Diffusion Tensor Imaging (DTI). DTI studies in SZ consistently report reductions in Fractional anisotropy (FA), a measure of fibre density, axonal diameter and myelination (Basser and Pierpaoli, 1996), primarily within the DLPFC and in its connections with the ACC and with subcortical (thalamus) and posterior cortical regions (Ellison-Wright and Bullmore 2009).

Although these fMRI and DTI changes are indicative of “dysconnectivity” (Bullmore et al., 1997; Friston and Frith, 1995; Stephan et al., 2006), the relationship between the neural dynamics and the wiring of the underlying anatomical network remain unclear. This is largely because single imaging modality analyses do not allow joint modelling of information from more than one data source. Joint independent component analysis (JICA) represents an advance in this respect as it provides a means to identify the sources of correlated information from different modalities (Calhoun et al., 2006; Sui et al., 2011). JICA is based on the simultaneous and empirically-driven interrogation of multimodal datasets and assumes that joint spatially independent sources are linearly mixed by a shared

parameter which “fuses” information from different modalities. This approach has been successfully applied to multimodal data analysis in SZ where it identified gray matter and functional networks contributing to case-control differences in neural engagement during an auditory discrimination task (Calhoun et al., 2006).

Within this context the aim of the present study was to investigate the relationship between anatomical connectivity and functional engagement within the working memory network in patients with SZ compared to controls. We focused on adolescents with SZ as adolescence is a critical period for the development of working memory (Conklin et al., 2007); gains in healthy adolescents have been associated with fMRI and DTI evidence of increased functional integration (Kwon et al., 2002; Finn et al., 2010) and enhanced white matter connectivity within the working memory network (Nagy et al., 2004). Therefore adolescence may be particularly informative with regards to structure-function relationships within the working memory network differentiating SZ patients from healthy controls. We acquired fMRI and DTI data from 25 adolescents with SZ and 19 healthy controls matched on age, sex and IQ in order to control for differences attributable to non-specific effects of demographic and cognitive factors (Tang et al., 2010). fMRI data were obtained during the 2-back working memory task which has been extensively used in SZ research (Glahn et al., 2005) thus providing a robust reference base for our study. Based on existing evidence we expected that JICA would identify joint components underlying structure-function differences between patients with SZ and controls (Calhoun et al., 2006; Sui et al., 2011). Specifically we hypothesised that abnormal engagement primarily in prefrontal regions in patients would be linked to FA reduction in white matter regions known to be traversed by tracts connecting these regions to posterior brain regions.

2. Methods

2.1. Participants

Twenty five adolescents fulfilling Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) (APA 1994) criteria for SZ and 19 demographically matched healthy controls participated in the study (Table 1). Detailed information about recruitment and assessment is presented in the *Supplemental material*. The study was approved by the Ethics Committee of the Institute of Psychiatry. All participants and their parents or guardians as appropriate provided written informed consent after detailed description of the study.

2.2. Neuroimaging

2.2.1 Two-back task—The 2-back task was administered as a block design, incorporating alternating active and control conditions. Participants were instructed to respond by button press at the target letter. In the control condition (0-back) the designated target was letter “X”. In the active condition (2-back), the target letter was defined as any letter that was identical to the one presented 2 trials back. In each condition a series of 14 letters were visually presented for 2 seconds each and responses were monitored via an MR compatible button box held in the subject’s dominant hand. There were 12 epochs in all, each lasting 30 seconds, with total experiment duration of 6 minutes. The ratio of target to non-target letters

presented per block ranged from 2:12 to 3:11. Response time to target letters and number of correct responses (accuracy) were recorded. To avoid confounding influences from poor motivation or poor task adherence we defined acceptable task performance during scanning on the basis of at least 80% accuracy in the 0-back and 60% accuracy in the 2-back condition. Three patients, but none of the controls, were excluded because they did not meet performance criteria.

2.2.2 Image acquisition—fMRI and DTI data were acquired during the same session on a 1.5-T imaging system (Signa GE Medical Systems, Milwaukee, Wisconsin). A total of 270 T2*-weighted echoplanar imaging (EPI) brain volumes depicting blood-oxygenation level-dependent (BOLD) contrast were acquired at each of 16 axial planes (echo time=40ms, repetition time=2s, voxel dimensions=3.75 × 3.75 × 7mm³, interslice gap=0.7mm, matrix size=64 × 64, flip angle=70°). Structural images were acquired using a 3D axial T1-weighted inversion recovery prepared Spoiled GRASS sequence for registration purposes (128 slices, echo time=5.1 ms, repetition time =2s, inversion time=450 ms, voxel dimensions=0.9375 × 0.9375 × 1.5 mm³, matrix size=256 × 192, field of view=240 × 180 mm², flip angle=20°, number of excitations=1).

DTI data were acquired using a multislice, peripherally gated EPI pulse sequence. Each DTI volume was acquired from 60 contiguous 2.5-mm thick slices with field of view 240 × 240 mm and matrix size 96 × 96, zero-filled to 128 × 128, giving an in-plane voxel size of 1.875 × 1.875 mm². Echo time was 107 msec and effective repetition time was 15 R-R intervals. At each location, 7 images were acquired without diffusion weighting, together with 64 diffusion-weighted images with diffusion gradients a diffusion weighting of 1300 sec mm² applied along directions uniformly distributed in space.

2.2.3 Unimodal fMRI and DTI Analyses—Image processing and analysis of fMRI data were implemented using Statistical Parametric Mapping 5 (SPM5) software (www.fil.ion.ucl.ac.uk/spm/) in a MATLAB 6 environment (The Mathworks Inc, Natick, Massachusetts). DTI processing was implemented using FMRIB's Diffusion Toolbox (FDT) (www.fmrib.ox.ac.uk/fsl). Detailed descriptions of the unimodal analyses are presented in *Supplemental Material*.

2.2.4 Joint Independent Component Analysis (JICA)—The JICA approach implemented here has been described in detail previously (Calhoun et al., 2006) and presented in *Supplemental Material*. Briefly, the fusion ICA toolbox (FIT, www.mialab.mrn.org/software/fit/) was used to perform data fusion of the first level fMRI images and the processed FA maps for each individual participant. FMRI and DTI maps were separately normalized to have the same average sum of squares. In-brain voxels were analysed and the two feature datasets were organized into a matrix. The Minimum Description Length criteria were used to estimate the dimensionality of the feature matrix (Calhoun 2001). The dimensionality of the data was first reduced with principle component analysis followed by ICA to decompose the reduced feature-matrix to maximally independent component images and subject specific mixing (loading) parameters. Group differences in loading parameters were examined using a t-test thresholded at p<0.05 corrected for multiple comparisons; only significant components were subsequently

examined. The joint ICA analysis produces a set of different regions for each type of data (referred to hereafter as JICA-fMRI and the JICA-DTI regions), which indicates which part of the combined data contributed significantly to the source. For display purposes JICA-fMRI and the JICA-DTI sources were converted to z-values and thresholded at $|Z| > 3.5$.

2.2.5 Examination of demographic and clinical factors—We examined the effect of age, IQ, antipsychotic medication, illness duration and psychopathology on fMRI, DTI and JICA parameters using the Statistical Package for Social Sciences for Windows—Version 15.0 (SPSS Inc, Chicago, Illinois). For fMRI and DTI, weighted parameter estimates and mean FA values respectively, were extracted from regions of interest (ROIs) created in each participant from suprathreshold clusters where group differences were noted. For the JICA, the loading parameters corresponding to significant components were extracted. The statistical threshold was adjusted to $p = 0.001$.

3. Results

3.1 Performance

Details of task performance are shown in Table 1. There was a significant main effect of condition on accuracy and response time (both $p < 0.001$) but not of diagnosis or condition by diagnosis interaction ($p > 0.1$).

3.2 Unimodal fMRI and DTI

Regions of suprathreshold group differences in brain activation and FA are shown in Table 2 and Figure 1. Further details are provided in the *Supplemental Material*.

3.3 JICA

Eight components were estimated from the data, of which one was significantly different between groups (Table 3, Figure 2). Loadings were significantly different (higher) in controls than patients ($p < 0.025$) (Supplementary figure 1). The JICA-fMRI source comprised regions of greater activation in controls in prefrontal and occipital regions and in the frontopolar region in patients. The JICA-DTI data source showed only regions of reduced FA in patients in the splenium of the corpus callosum and the posterior cingulum. Voxels surviving the threshold for the fMRI and DTI part of the joint source were sorted in descending order by their component values. This procedure resulted in two sets of voxel coordinates. By pairing these two voxel sets we generated single-subject 2D histograms of fMRI signal (as estimated by the SPM contrast image) versus DTI signal (as estimated by the FA map) (Supplementary Figure 2). Using the within-group average of these histograms (Supplementary Figure 2), the control group average was subtracted from the patient group average (Supplementary Figure 2). The marginal estimated distributions were also computed (Supplementary Figure 1).

3.4 Effect of demographic and clinical factors

None of the demographic and clinical measures had a significant effect on the imaging parameters examined.

4. Discussion

We used joint independent component analysis (JICA) to identify regions of joint, multimodal brain sources within the working memory network in patients with SZ compared to controls. The JICA-fMRI source implicated prefrontal and occipital regions where patients showed relative hypoactivation, and frontopolar regions where they expressed relative hyperactivation. The JICA-DTI source identified regions of reduced FA in patients in the cingulum and the splenium. The JICA-fMRI and JICA-DTI have the same contribution to inter-subject covariation, which reflects linked functional and white matter changes.

4.1 Functional abnormalities in the working memory network associated with SZ

Conventional unimodal fMRI analysis of our data revealed hypoactivation in patients throughout the working memory network including reduced prefrontal engagement consistent with previous literature (Glahn et al., 2005; Pauly et al., 2008; Sugranyes et al., 2011). The DLPFC and medial prefrontal regions implicated here are respectively involved in manipulation of task relevant information and maintenance of visuospatial attention during working memory tasks (Champod and Petrides, 2010; Fletcher and Henson, 2001; Smith and Jonides, 1998). These processes are considered of particular relevance to the pathophysiology of SZ (Cannon et al., 2005) while more simple mnemonic functions (e.g. supporting delayed match to-sample performance) are not associated with significant differences between SZ and controls regardless of age (Minzenberg et al., 2009; White et al., 2011). Additional hypoactivation was noted in ACC, parietal cortices, basal ganglia and thalamus, regions postulated to be functionally connected with the DLPFC and to subserve performance monitoring and encoding (Meda et al., 2011). Reduced engagement in patients compared to controls was also present in temporal and cerebellar regions, recently recognised as being respectively involved in encoding and target recognition during working memory.

4.2 Reduced FA associated with SZ

In accordance with previous literature, patients with SZ showed reductions in FA mainly within the prefrontal and temporal white matter as well as the cingulum and splenium of the corpus callosum (Arnone et al., 2008; Douaud et al., 2009; Ellison-Wright and Bullmore 2009; Fitzsimmons et al., 2009; Kumra et al., 2005; Mitelman et al., 2007; Patel et al., 2011). It has been hypothesised that white matter deficits in prefrontal regions impact on their connection to the cingulate and thalamus while deficits in the temporal white matter affect connections between frontal, limbic, hippocampal and occipital regions. Consistent with this hypothesis we found FA reductions in the white matter tracts traversed by fibers connecting medial occipital and parietal regions, in the fornix and parahippocampal white matter and in the cingulum.

4.3 Function-structure relationships

The JICA allowed us to detect regions that represent joint, fMRI-DTI brain sources that differ between the groups. The JICA-DTI source identified a significant contribution by white matter tracts traversing the splenium and the posterior cingulum. Although multiple

regions of the corpus callosum have been reported as abnormal in SZ the largest effect size of FA reductions has been found in the splenium (Patel et al., 2011). Of particular relevance is the longitudinal study by Keller and colleagues (Keller et al., 2003) who reported failure of normal callosal growth in patients with early onset SZ resulting in area reductions, particularly in the splenium. The splenium receives fibers from the caudal two-thirds of the temporal lobe and from the medial occipital cortex (Dougherty et al., 2005). It is therefore likely that the reduced activation within the cuneus identified by the JICA-fMRI data source may be directly linked to abnormalities within fibers traversing the splenium. Similar considerations apply to the contribution of reduced FA in the posterior cingulum identified by the JICA-DTI data source. The cingulum is the major association bundle of the brain consisting of short commissural and longer cortical association fibers (Mufson and Pandya, 1984). Although these fibers intermingle they also show distinct topography. The posterior cingulum, implicated in this study, includes fibers from frontal regions travelling to the posterior cingulate gyrus and medial parietal cortex and fibers connecting the posterior cingulate gyrus with hippocampal/parahippocampal regions and the posterior parietal cortex (Mufson and Pandya, 1984; Petrides and Pandya 2006, 2007). The prefrontal and ACC hypoactivation in patients identified in the JICA-fMRI data source is highly consistent with that expected from abnormalities in white matter tracts traversing the posterior cingulum. Patients showed relative hyperactivation in the right dorsomedial frontopolar region. In a meta-analysis of n-back studies, Glahn and colleagues (2005) also noted relative hyperactivity in SZ patients compared to controls in an overlapping region centred more dorsally and medially to the one identified here. The authors considered this as a compensatory response reflecting increased retrieval effort in patients. Our results point to another interpretation. Between the ages of 8-20 years the cortical thickness of the frontopolar region decreases in response to maturational events in gray and white matter leading to improved functional efficiency (O'Donnell et al., 2005, Sowell et al., 2001). Based on the JICA analysis it is plausible that deficits in frontal association fibers coursing through the splenium and cingulum may impact on the maturational trajectory resulting in reduced integration of the frontopolar cortex within the working memory network.

4.4 Methodological considerations

Several methodological issues need to be considered. First, although we describe function-structure relationships consistent with the notion of abnormal connectivity neuroimaging techniques cannot identify the precise neuropathological correlates involved. FA reductions are thought to arise from myelin abnormalities, alterations in axonal packing density or disrupted fibre alignment. Changes in synaptic function may also contribute to altered anatomical or functional connectivity (Stephan et al., 2006). Second, patients were medicated with antipsychotics which could have contributed to functional and structural group differences. However this is unlikely as no effect of medication was detected. Thirdly, although patients were in clinical remission and engaged in the task their performance was numerically (albeit not statistically) below that of the healthy controls. Performance is particularly relevant in the interpretation of group differences in functional activation patterns (Manoach et al., 2003). However, nearly all working memory studies in SZ (Glahn et al., 2005) have also found underperformance in patients. One could argue that this task may tap into core capacity limitations inherent to SZ and that the functional abnormalities

detected represent their neural signature. Fourth, patients in this study manifested SZ during adolescence. Examination of this age group reduces potential confounds relating to chronicity and prolonged antipsychotic exposure and maximises the ability to detect fMRI-DTI relationships since adolescence is a period of major remodelling affecting brain connectivity both in healthy (Finn et al., 2010; Kwon et al., 2002) and SZ adolescents (Gogtay and Thompson, 2010). The consistency between the findings of the unimodal analyses in this study and those reported in adult onset SZ is particularly reassuring with regards to generalizability of our results. Fifth, JICA assumes that the voxels and features are independent and identically distributed. Although this is probably not the case all ICA models employ this assumption and maintain acceptable performance (Calhoun et al., 2001; Calhoun et al., 2006). Another assumption is that relationships between data sources are linear, so any nonlinear relationships may not be captured by this approach.

5. Conclusions

We identified key components of joint multimodal brain sources contributing to dysconnectivity in SZ during working memory. It would be interesting to test the reproducibility of our results in a larger sample of patients with SZ using other multimodal techniques as spatial correlation (Michael et al., 2010) or parallel ICA (Liu et al., 2009). Furthermore JICA and similar analytical methods may be used to incorporate other types of information, such as candidate genes for SZ. This approach would allow identification of convergent effects of these genes on neural systems, particularly since a number of them (e.g. ZNF804A, NRG1) are likely to impact on experience dependent connectivity, linking functional and structural changes in SZ (Meyer-Lindenberg 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Regions of significant group differences derived from unimodal analyses. (a) Functional magnetic resonance imaging (fMRI) results corresponding to the 2-Back>0-Back contrast; threshold: $t > 3.1$, $p < 0.001$ uncorrected for multiple comparisons, (b) Diffusion tensor imaging (DTI) results, threshold: $t > 3.5$, $p < 0.05$ corrected for whole brain comparisons.

Figure 2.

Joint source maps for functional magnetic resonance imaging (fMRI) (a) and diffusion tensor imaging (DTI) (b), representing the areas of brain activation corresponding to the component which had a significant group effect. Images were thresholded at $Z > 3.5$ and $p < 0.05$ corrected for multiple comparisons.

Table 1
Sample Characteristics

	Patients with Schizophrenia (n=22)	Healthy Controls (n=19)
Demographic features		
Age at scan (years)	17.1 (1.5)	16.5 (1.98)
Gender (male/female)	14/8	11/8
Handedness (right/left)	22/0	17/2
WRAT3 score	96.7 (15.29)	97.63 (9.88)
Clinical Characteristics		
Age of illness onset (years)	14.7 (1.5)	-
GAF	62.35 (12.04)	-
PANSS Total	44.23 (7.55)	-
PANSS Positive	8.86 (2.10)	-
PANSS Negative	12.54 (3.33)	-
Task performance		
Zero-back accuracy (% correct)	96.48 (6.88)	99.31 (1.63)
Two-back accuracy (% correct)	84.66 (13.32)	94.08 (10.51)
Zero-back response time (seconds)	0.52 (0.89)	0.47 (0.07)
Two-back response time (seconds)	0.67 (0.18)	0.57 (0.10)

There were no group differences in age, gender, handedness and IQ (all $p>0.34$) or performance ($p>0.1$). Continuous variables are shown as mean (standard deviation); WRAT3=Wide Range Achievement Test 3; GAF=Global Assessment of Functioning; PANSS=Positive and Negative Syndrome Scale

Table 2
Regions of group differences in unimodal analyses

Unimodal fMRI results					
Region	Brodmann Area	Laterality	Cluster size	T - value	Peak coordinates
Medial Frontal	8/6	Left	34	3.60	-12, 13, 48
Middle Frontal	46	Left	49	4.09	-34, 40, 22
Supplemental Motor Area	6/32 6	Right	30	3.65	24- 18, 42
			25	3.64	30, -12, 60
Anterior Cingulate	32	Left	53	3.63	-12, 24, 26
	24	Right	12	3.24	14, 18, 34
Posterior Cingulate	29	Left	24	3.39	-20, -42, 20
Middle Temporal	20	Left	122	4.39	-46, -26, -14
Superior Parietal	7	Right	85	4.76	28, -50, 60
Inferior Parietal	40	Left	20	3.23	-56, -44, 30
Putamen	-	Left	123	3.74	-20, 6, 12
Thalamus	-	Right	16	3.36	16, -13, 7
Cerebellum	-	Left	193	4.09	-6, -35, 19

Unimodal DTI results					
Region	Main Fasciculi	Laterality	Cluster size	T -value	Peak coordinates
Inferior frontal	Inferior fronto-occipital	Left	1773	4.81	-33, 35, 13
			669	4.38	-37, 10, 13
	Uncinate	Left	825	4.07	-35, -3, -10
Cingulate	Cingulum	Right	1527	5.21	27, -4, -24
		Left	654	3.93	-14, -3, 40
Superior temporal	Inferior longitudinal	Right	1218	4.92	46, -28, 3
Parahippocampal	Cingulum, fornix	Left	5186	4.72	-16, -25, -6
	Fornix	Right	1588	4.47	16, -24, -5
	Cingulum	Right	696	4.41	17, -30, -7
Corpus Callosum	Genu	Right	548	5.04	7, -8, 64
	Splenium	Right	2838	4.18	8, -57, 29
		Left	8611	4.79	-20, -46, 27
Cerebellum	-	Right	2295	4.27	35, -54, -32
		Left	1002	4.22	-36, -48, -33

fMRI= functional magnetic resonance imaging; DTI= diffusion tensor imaging; peak coordinates in Talairach space

Table 3
joint independent component analysis of fMRI and DTI

fMRI source					
Region	Brodmann Area	Laterality	Cluster size	T - value	Peak coordinates
Schizophrenia < Healthy Controls					
Anterior Cingulate	32	Left	0.7	5	-2, 25, 39
	32	Right	0.4	4.2	0, 18, 49
Supplementary Motor Area	6	Right	0.7	4.9	4, -5, 61
Inferior Frontal	47	Left	0.2	4.6	-50, 15, -6
Cuneus	18	Left	0.2	4.5	-4, -83, 19
Schizophrenia > Healthy Controls					
Superior Frontal	10	Right	0.8	5.4	20, 57, 21
	10	Right	0.1	4.8	24, 57, 21

DTI source					
Region		Laterality	Cluster size	T -value	Peak coordinates
Schizophrenia < Healthy Controls					
Cingulum	-	Left	0.2	4.0	-6, -32, 22
	-	Left	0.1	3.6	-12, -32, 26
	-	Left	0.1	3.6	-12, -36, 15
	-	Right	0.3	3.9	8, -34, 22
Corpus Callosum, Splenium	-	Left	1.5	4.3	-4, -34, 18
	-	Right	1.3	4.3	4, -36, 17
Schizophrenia > Healthy Controls					
No suprathreshold clusters					

fMRI: functional magnetic resonance imaging; DTI: diffusion tensor imaging; Peak coordinates in Talairach space