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Altered default mode network activity and cortical thickness as vulnerability indicators for SCZ: a preliminary resting state MRI study

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Abstract. – OBJECTIVE: Alterations in brain function in patients with schizophrenia (SCZ) and other neuropsychiatric disorders are evident not only during specific cognitive challenges, but also from functional MRI data obtained during a resting state. Patients with chronic SCZ have shown deficits in default mood network (DMN) and gray matter volume in resting-state functional magnetic resonance imaging (rs-fMRI). However, cortical thickness and surface area in first-episode schizophrenic patients have rarely been investigated.

PATIENTS AND METHODS: In the present study, we applied independent component analysis (ICA) to a series of rs-fMRIs of 15 SCZ patients and 15 matched healthy controls. The data were analyzed using MELODIC of FMRIB's Software Library (FSL version 5.9; www.fmrib.ox.ac.uk/fsl) to identify large-scale patterns of temporal signal-intensity coherence.

RESULTS: Patients with SCZ showed significantly higher functional connectivity in the DMN, auditory network, and cerebellum network (p=0.049, p=0.05, and p=0.007, respectively) than matched healthy controls. The patients also exhibited significantly less cortical thickness, primarily in the bilateral prefrontal and parietal cortex, and higher thickness in the bilateral anterior temporal lobes, left medial orbitofrontal cortex, and left cuneus than the matched healthy controls.

CONCLUSIONS: These results indicate that significantly abnormal DMN connectivity and cortical thickness contribute to local functional pathology in patients with SCZ.

Key Words:
SCZ, MRI, Hippocampus, Default mode, Cortical thickness.

Introduction

Shizophrenia (SCZ) is a chronic, complex, long-term psychiatric disorder characterized by perceptual, behavioral, and cognitive deficits and abnormal emotional regulation, accompanied by hallucinations, delusions, negative symptoms, and disorganized thinking and speech[1,2]. Evidence is accumulating that patients with SCZ present with aberrant functioning of the default mode network (DMN)[3-5]. The DMN is one of the most studied brain networks and has become a central topic in research on SCZ[6]. It is a widespread interconnected network that encompasses multiple core hubs of brain regions, including the posterior cingulate cortex (PCC), the precuneus (PCu), the medial prefrontal cortex (mPFC), and the bilateral inferior parietal lobule (IPL). It expands to the posterior temporal regions around the temporoparietal junction (TPJ), as well as the hippocampus, the parahippocampal, and adjacent regions in the

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medial temporal lobe (MTL) and lateral temporal cortex (LTC), and it extends towards the temporal pole (TP)[7-11]. The DMN has repeatedly shown to be deactivated during external goal-oriented cognitive tasks and highly activated in a resting state and intrinsic mental processing[7]. Moreover, this network has been shown to contribute to different aspects of self-referential or self-generated thought and reflective activity[10,12-14].

Increasing numbers of brain imaging studies[11,15-17] have investigated the role of DMN disintegration in SCZ. Significant disruptions to DMN activity have been reported to correlate with different symptoms of SCZ, including positive and negative symptoms[18-20]. Suppressed DMN activity during the performance of a wide range of cognitive tasks has also been observed in patients with SCZ; this might be inferred to be the root of cognitive deficits in such patients[21,22]. Similarly, a recent study[23] has reported that disruptions to the frontoparietal network and the DMN were associated with the metacognitive deficits that are clinically observed in patients with SCZ. Investigations using resting-state functional connectivity (rs-FC) magnetic resonance imaging (MRI) have shown altered functional connectivity between the medial prefrontal cortex and the bilateral anterior cingulate cortex within the DMN. This correlates significantly with the poorer sustained attention observed in patients with SCZ compared to healthy controls[16]. Decreased DMN connectivity is associated with poorer clinical outcomes in patients with SCZ. In addition, reduced functional connectivity within the DMN has been found to correlate with the severity of positive symptoms (in contrast to negative symptoms) of SCZ[24]. These findings together suggest the importance of disrupted activity and functional connectivity in the DMN as one of the underlying pathological mechanisms of SCZ. Therefore, DMN dysfunction has clinical implications as an indicator of an individual's vulnerability to SCZ[15,17,23,25]. In addition to alterations in DMN functional connectivity, considerable evidence indicates that SCZ is characterized by excessive loss of cerebral gray matter volume (GMV) and surface area of certain brain regions[26-30]. Converging structural brain imaging studies have revealed excessive cortical thinning in widespread areas, with marked reductions in the frontal and temporal lobes and in the parietal and occipital cortices[31-34]. Excessive widespread cortical thickness reductions in the fronto-temporoparietal region, insular sulcal flattening, and gyrification reduction in the frontal cortex have also been detected in patients with SCZ[34]. These results suggest that cortical morphology might serve as a marker of increased genetic risk for SCZ and could underlie the cognitive deficits in patients with SCZ[34]. Combining resting-state functional and structural imaging could enrich our understanding of the pathogenesis of SCZ. Therefore, investigating cortical thickness and DMN characteristics can help elucidate the underlying pathophysiological mechanisms and risk indicators of SCZ. The present study aimed to compare DMN functional connectivity and cortical thickness in patients with SCZ and in matched healthy controls. Accordingly, we applied independent component analysis (ICA) to resting-state functional magnetic resonance imaging (rs-fMRI) data and compared the DMN connectivity of healthy controls to that of patients with SCZ. We also compared the cortical thickness and surface area of the two groups.

Patients and Methods

Participants

The study was approved by the Institutional Review Board of King Khalid University Hospital. Participants included two groups: one group of healthy controls (n = 15) recruited via the hospital's volunteer recruitment system and a group of patients with SCZ (SCZ; n = 15) recruited through local psychiatric clinics and hospitals. The average age of participants was 33.14 ± 9.96 yrs. (Table I). All subjects provided written informed consent to participate before the study began. Both groups were outpatients and had been clinically stable for at least two weeks. Table I shows the demographic data of the subjects.

Clinical Assessment

Participants in the SCZ group were diagnosed by experienced psychiatrists based on the DSM-IV criteria[35].

Participants were excluded if they: (a) had experienced any substance dependence or severe/moderate substance abuse (according to the DSM-IV criteria) in the six months prior to the study; (b) were clinically unstable or had experienced a severe medical disorder unrelated to SCZ in the previous six months; or (c) had a history of loss of consciousness or head injury with documented neurological problems.

Trained research assistants used the Assessment of Negative Symptoms (SANS; includes subscales for flat affect, alogia, anhedonia, and amotivation) and the Scale for the Assessment of Positive Symptoms (SAPS; includes subscales for hallucination and delusion), disorganization (including subscales for formal thought disorder, bizarre behavior, and attention) to assess psychopathology[36].

Image Acquisition

A Siemens Magnetom Verio 3T MRI clinical scanner (Siemens AG, Healthcare Sector, Erlangen, Germany) and a 12-channel phased-array head coil were used to acquire the following: (1) T1-weighted 3D magnetization-prepared rapid gradient-echo imaging (MPRAGE): TR = 1600 ms, TE = 2.19 ms, inversion time = 900 ms, flip angle = 9°, acquisition plane = sagittal, voxel size = $1 \times 1 \times 1$ mm^3, FOV = 256 mm, acquired matrix = 256×256, acceleration factor (iPAT) = 2; (2) Fluid attenuated inversion recovery (FLAIR): TR = 9000 ms, TE = 128 ms, inversion time = 2500 ms, flip angle = 150°, acquisition plane = axial, slice thickness = 5 mm, FOV = 220 mm, acquired matrix = 256 × 196, acceleration factor (iPAT) = 2; and (3) a rs-fMRI sequence as in the following an echo planar imaging (EPI) based sequence with the following acquisition parameters: 64 2-mm thick axial slices with a field of view (FOV) of 224 x 224 and a matrix size of 112 x 112. The TE and TR were 30 ms and 1400 ms, respectively. The acceleration factor (iPAT) was 4.

Data Analysis

The Computational Anatomy Toolbox (CAT12: http://www.neuro.uni-jena.de/cat), an extensive toolbox of Statistical Parametric Mapping software (SPM12: http://www.fil.ion.ucl.ac.uk/spm) running in Matlab R2018b has been used to derive morphometric measures of the whole brain calculating the differences in cortical thickness between SCZ patients and healthy control groups. The pre-processing steps were carried out according to the default settings of the fully automated SBM method that is described in detail in the manual of CAT12. In the SBM method, the GM-WM boundary for each hemisphere was determined, and the cortical thickness and central surface were calculated through the projection-based thickness (PBT) method[37]. The left and right cortical thickness maps were then resampled into template space and smoothed with a Gaussian kernel of 15-mm FWHM.

Results

The sociodemographic profiles of the participants are shown in Table I.

The SCZ group showed significantly higher functional connectivity in the default mood network (DMN), specifically in the right temporal pole (p=0.002), than the matched healthy controls.

In addition, the SCZ patients had lower gray matter density than the control subjects in various brain regions, including the left supramarginal gyrus (p=0.01), the left and right insular cortices (p=0.03), the left precentral gyrus (p=0.04), and the right cingulate gyrus (p=0.04).

Compared to the controls, the SCZ group exhibited significantly reduced cortical thickness, primarily in the right dorsolateral prefrontal cortex (DLPFC), the left precentral gyrus, the left orbitofrontal cortex (OFC), the left inferior frontal gyrus pars triangularis, and the right precentral and postcentral gyri (p=0.05, corrected for multiple comparisons; Figure 1, Table II). In addition, significant cortical thickening was observed in the bilateral anterior temporal lobes, the left medial orbitofrontal cortex (med-OFC), and the left cuneus of the SCZ group compared to the controls (p=0.05, corrected for multiple comparisons; Figure 2). There was a significant difference in surface area between the two groups.

Discussion

The purpose of this study was to investigate functional connectivity within the DMN and to measure cortical thickness in patients with SCZ. Our findings showed significantly higher functional connectivity within the DMN, particularly in the right temporal pole, in patients with SCZ than in matched healthy controls. The patients with SCZ also presented with higher functional connectivity between distinct brain networks,

Table I. Anthropometric data of SCZ and control group.

Parameters	Control (n=15)	SCZ (n=15)
Age	28.8±8.9	33.9±9.9
Height	170±7.1	154±45
Weight	74±15	77±29

Vales are presented in Mean ±SD.

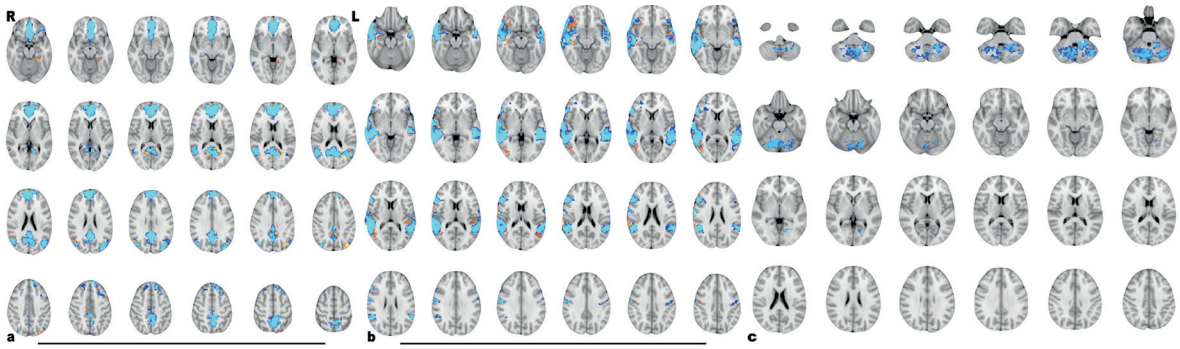

Figure 1. Statistical grand average maps of ICA networks of; (a) DMN, (b) auditory and (c) cerebellum networks overlaid on 24 axial slices of the MNI152_T1_2mm standard image included in FSL. The (red-yellow) color show ICA maps of control group and the (blue-lightblue) color show ICA maps of SCZ patients group, SCZ patients showed greater connectivity in all three networks (p=0.049, p=0.05 and 0.007 respectively).

specifically the auditory and cerebellum networks. These findings are in line with other recent studies indicating altered functional connectivity between distinct networks and within networks in patients with SCZ; these alterations have been observed in the frontoparietal[23], subcortical[17], and cerebellum networks[42]. One possible explanation for the current findings is that increased resting-state functional activity in the DMN might reflect hyperactivity in the brain's self-referential processing[43]. Higher DMN activity might help elucidate common symptoms of SCZ, such as rumination and negative symptoms, which have been repeatedly associated with high DMN resting-state connectivity[44-47]. Another explanation is that a failure to inhibit DMN activity might be attributed to the interference of intrinsic mentation and awareness processing[48,49]. It is possible that this high functional connectivity within the DMN might relate to an increase in internally directed thought[46,50,51], an explanation that correlates with the clinical scores of patients with SCZ reported in previous studies[18-20,24].

Diverse evidence[52,53] from neurophysiological and neuroimaging research has highlighted abnormalities in the morphology, physiology, and function of medial temporal lobe (MLT) structures, including the hippocampus, para hippocampus, amygdala, and entorhinal and perirhinal cortices in psychotic illness. Abnormalities in the medial temporal lobe have been identified before the onset of overt psychotic symptoms in clinical high-risk individuals for psychosis illness[52,54]. It is worth mentioning that individuals who experienced one or more of the prodromal symptoms, which are characterized by attenuated psychotic symptoms, including a brief psychotic episode, paranoid ideation, odd beliefs, subthreshold hallucinations and delusions, or display a social and communication deficits are considered to be at clinical high risk for psychosis[55,56]. In a cross-sectional and longitudinal MRI study, high-risk individuals who developed psychotic symptoms, compared to those who did not, showed gray matter changes in the medial temporal structures, inferior frontal cortex, and cingulate cortex during the transition to psychosis[57].

Table II. P values and MNI coordinates of cluster peak regions.

Cluster Index	$P_{FEW\ corrected}$	T	Z	X (mm)	Y (mm)	Z (mm)	Region Name
1	0.001	6.25	4.91	26	28	37	R Middle Frontal Gyrus
2	0.01	5.73	4.62	-52	5	22	L Precentral Gyrus
3	0.000	5.68	4.59	15	20	57	R Superior Frontal Gyrus
4	0.007	5.43	4.45	23	2	54	R Superior Frontal Gyrus
5	0.023	5.33	4.39	-38	39	30	L Frontal Pole
6	0.041	5.18	4.30	42	34	-14	R Frontal Orbital Cortex
7	0.038	5.07	4.23	-13	28	52	L Superior Frontal Gyrus

We also observed significantly lower cortical thickness in the patients with SCZ, primarily in the right dorsolateral prefrontal cortex (DLPFC), the left precentral gyrus, the left orbitofrontal cortex (OFC), the left inferior frontal gyrus (pars triangularis), and the right precentral and postcentral gyri. Significant cortical thickening was detected in the bilateral anterior temporal lobes, the left medial orbitofrontal cortex (med-OFC), and the left cuneus in the patients with SCZ. Previous studies[28,29,31-34] have demonstrated a similar pattern of reduced cortical thickness, which may indicate that cortical structural abnormalities could indicate a genetic risk of SCZ.

Evidence from a variety of studies on psychotic disorders has shown a pattern of disorder-associated morphological changes; thereby, the pattern of structural changes differs according to the type of psychotic illness[58-61]. Our previous study[62] showed abnormal shape patterns in the right hippocampus, left and right putamen, left caudate, right pallidum. In contrast, the volume decrease was shown in SCZ patients in the left thalamus[62].

Grey matter decreases in multiple cortical regions, including the frontal and temporo-limbic regions but not the medial temporal region, were more prominent in patients with chronic psychosis than in patients with first-episode psychosis[60,61]. This is supported by a previous meta-analysis[63] of longitudinal MRI studies which showed no evidence of medial temporal lobe abnormalities involvement in chronic SCZ. These findings suggest that related-psychotic pattern of abnormalities or changes differ according to the type of disorder, which might interpret the early symptoms and severity according to the affected brain regions[63-65].

Divers cortical regions, including OFC and fusiform gyrus, were found to be significant contributors to vulnerability to psychosis, particularly in light of emotional processing dysfunction[65-68]. The OFC is a crucial node for emotional information processing[69]. The extensive connection between the orbitofrontal cortex and other brain regions involved in emotion, including the amygdala, suggests significant involvement of the OFC in multiple cognitive functions, such as emotional decision-making, impulse control, social behavior and mood regulation[70-72]. The fusiform gyrus is a critical region in recognizing and processing faces and is, therefore, important in integrating perception and emotion[73]. Reduced volume of the fusiform gyrus was extensively observed in psychosis and was significantly correlated with negative psychotic symptoms such as anhedonia, emotional blunting, apathy, lack of motivation, and social interest[67,74]. Such volumetric reduction in the fusiform gyrus might be associated to a failure in facial recognition and affective information processing and, therefore, might lead to inappropriate social interaction and communication seen in patients with psychosis[74].

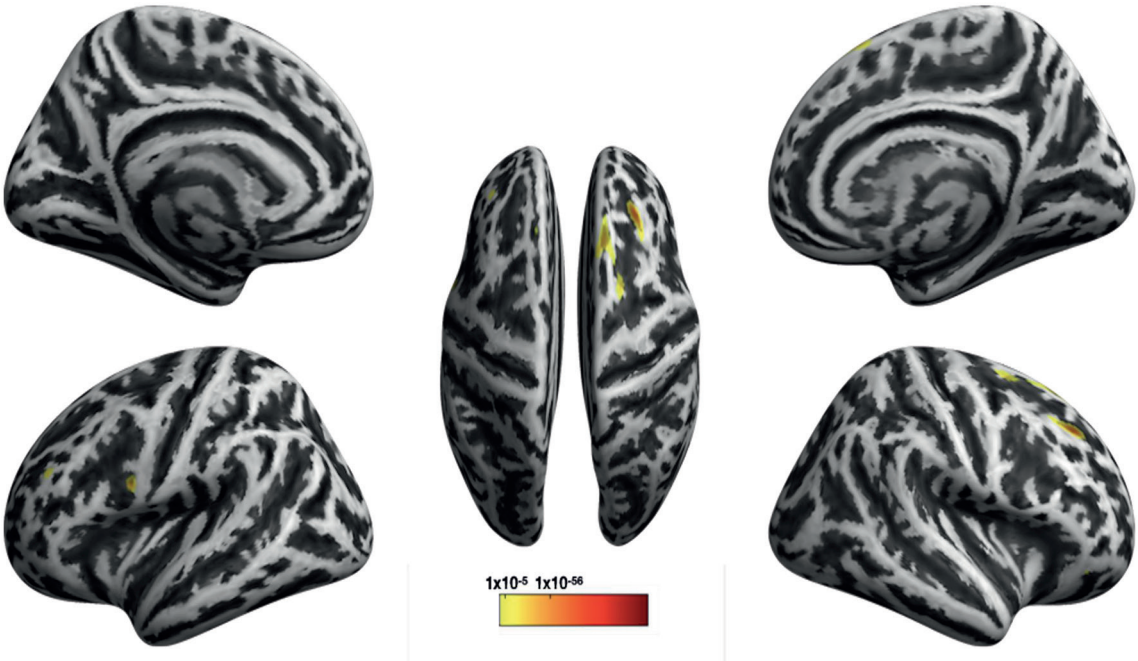

Figure 2. T-statistic map of group difference in cortical thickness.

These converging results might suggest that morphological changes in different brain regions can predict the pattern of emotional information processing in psychotic disorders[66,72,75].

Wannan et al[76] have reported that the frontal and temporal cortical regions, which show pronounced reductions in cortical thickness in patients with SCZ, have stronger interregional anatomical connectivity. This suggests that the topography of cortical thickness reductions in patients with SCZ can be explained by structural network topology and not by spatial proximity to the pathologically affected regions of the brain. These findings might indicate that functional connectivity within the resting-state DMN[18,77,78] and reductions in cortical thickness[29,31-34] may serve as indicators of vulnerability to SCZ.

Conclusions

One major strength of this study is its combination of resting-state functional and structural imaging to investigate the pathophysiological mechanisms and risk indicators underpinning SCZ. However, some limitations should be considered in interpretations of the current results. Our sample size is small and has a relatively large age range. Moreover, the investigated factors (resting-state DMN functional connectivity and cortical thickness) were not correlated with the participants' clinical profiles. Integrating and correlating different types of functional and structural imaging measures with clinical scores or symptoms in SCZ could provide different findings. Further studies on a larger population size would shed more light on the genetic risks and predictors of SCZ. In conclusion, resting-state functional magnetic resonance imaging of patients with SCZ showed that these patients present with deficits in DMN functional connectivity and reduced cortical thickness in several widespread regions of the brain.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgments

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Data availability statement

Data are available on request.

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