Intrinsic Brain Abnormalities in Violent Offenders with Schizophrenia: A Resting-State Functional MRI Study

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Purpose: Schizophrenia is a mental disorder characterized by problems with thought processes and by poor emotional responses. There is much evidence that schizophrenia patients have an increased risk for aggression and violent behavior, including homicide. Low-frequency (0.01 – 0.08 Hz) fluctuations of the blood-oxygenation-level-dependent (BOLD) signal in resting state fMRI data are thought to reflect regional spontaneous neural activity while Functional connectivity (FC) were efficient approach to reveal the brain activity between two remote areas. Though a lot of studies had been carried out in the past years using functional MR to explore the neural activity abnormalities in schizophrenia, few articles had focus on the subgroup of patients with severely violence behavior without drug abuse. In the current study, we aim to perform a tentative study on neural activity abnormalities in schizophrenia patients with severely violent behavior using resting state fMRI.

Methods: Eighteen male violent offenders appraised as schizophrenia (VS) according to DSM-IV were recruited from the forensic psychiatry department (mean age = 38.17±10.42years) and 24 age and handedness matched male healthy controls (HC) (mean age=35.83±14.25 years) were also recruited through advertisement. Modified Overt Aggression Scale (MOAS), Wisconsin Card Sorting Test (WCST) and Positive and Negative Syndrome Scale (PANSS) for schizophrenia were used for clinical evaluation in all the participants. The MRI examinations were performed via a 3-Telsa GE MRI system with an 8 channel phase array head coil. The resting-state fMRI sensitized to changes in BOLD signal levels were obtained via a GE-EPI sequence (TR/TE=2000/30msec,flip angle=90°, slice thickness=5mm with no gap, 30 axial slices, 200 volumes in each run). Subjects were instructed to relax with their eyes closed without falling asleep during MR examination. DPARSF software was used to calculate the parametric maps of Amplitude of Low Frequency Fluctuations (ALFF) (0.01 – 0.08 Hz). Head translation movement of all participants was <1.5 mm and rotation was < 1.5°.Then, the FC maps were generated using a seed correlation approach based on regions with altered ALFF. A reference time series for each seed was extracted by averaging the rfMRI time series of voxels within each seed. Correlation analysis was carried out between each seed and the filtered time series in the rest of the brain. The correlation coefficients in each voxel were transformed to z values, and then spatial smoothing (8-mm full width half-maximum).Voxel-based analysis of the ALFF and FC maps between the violent schizophrenia patients and the healthy controls was performed using two sample t-test in SPM. The AlphaSim-corrected p value of less than 0.05 at cluster-level was deemed to be significant for the analysis. The ALFF values at significant different regions were extracted to perform the correlation with the clinical and behavioral assessment scales.

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	VS (n = 18)		NN (n = 24)		Significance	
	Mean	SD	Mean	SD	t	P value
Age (yrs)	38.17	10.42	35.83	14.25	0.59	0.56
MOAS	27.06	8.47	5	3.26	11.7	<0.001
WCST						
Total Correct	24.67	10.2	40.33	3.97	-6.89	<0.001
Categories Completed	1.94	1.16	4	0.29	-8.35	<0.001
Total Errors	23.22	9.82	7.67	3.97	7.05	<0.001
Perseverative Errors	15.67	11.48	4.13	2.4	4.81	<0.001
Nonperseverative Errors	7.56	4.5	3.5	2	3.94	<0.001
PANSS						
General	38.33	3.29	—	—	—	—
Positive	30	5.01	—	—	—	—
Negative	26.11	5.76	—	—	—	—
Supplementary	11.33	3.23	—	—	—	—

Results: Related to controls, VS patients showed worse performance in WCST Compared with the healthy controls (**Table 1**).The violent schizophrenia group demonstrated significant increased ALFF in bilateral striatum and decreased ALFF in right precuneus and left cerebellum (**Figure1**). Specifically, VS group showed significant negative correlations of ALFF value in the precuneus with PANSS-Positive score(r=-0.519, p=0.027) (**Figure.1**).The FC analyses showed comparing with healthy controls, VS group showed increased FC in left orbitofrontal cortex(OFC) and bilateral middle occipital when seed were put at precuneus, and decreased FC in left middle temporal gyrus and bilateral insula when seed were put at cerebellum (**Figure 2**).

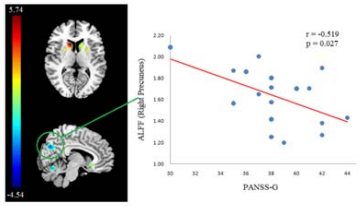

Fig 1. The increased(red) and decreased(blue) regions in the violent Offenders with Schizophrenia patients comparing to healthy controls and the correlation between PANSSP-P score and ALFF value in precuneus.

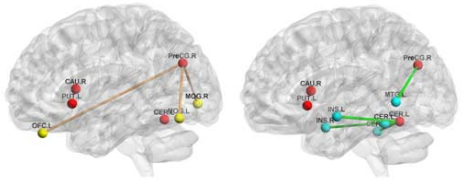

Fig 2.natomic replicas show differences of FC between patients with VS and healthy control subjects. The red nodes represent the seed areas of FC. The yellow nodes and orange lines and blue nodes and green lines represent, respectively, increased and decreased FC in patients with VS relative to healthy control subjects. Left: *CAU.R* = caudate,right; left; *PUT.L* = putaman, left; *PreCG.R*= precuneus, right; *CER.L* = cerebellum, left; *MOG.R*=middle occipital gyrus, right; *MOG.L* = middle occipital gyrus, left; *OFC.L* = orbitofrontal cortex, left. Right: *CAU.R* = caudate,right; left; *PUT.L* = putaman, left; *PreCG.R*= precuneus, right; *CER.L* = cerebellum, left;*MTG.L* = middle temporal gyrus, left;*INS.L* = insula, left; *INS.R* = insula, right.

Discussion and conclusion: Relative to healthy controls, the VS group showed significantly decreased ALFF in the precuneus, which is an important area in the default mode network (DMN). The precuneus is involved in several higher-order functions, such as visuospatial imagery, episodic memory retrieval, and self-processing operations. Some of these functions are severely disturbed in schizophrenia. The role of cerebellum in schizophrenia has been highlighted by the hypothesis of "cognitive dysmetria," which suggests a general dyscoordination of sensorimotor and mental processes[1].The present study has showed decreased ALFF activity in left cerebellum in VS group compared to healthy controls. This result is consistent with previous studies and may be associated with cognitive and behavioral abnormalities in schizophrenia. In addition, the VS patients showed increased ALFF activity of bilateral striatum, which belongs to cortical-striatal circuitry is known for its role in emotion regulation[2]. We postulate that the abnormality in striatum may play a role in the deficit of emotional control and thus cause the violent behavior in those schizophrenia patients. Interestingly, despite the decrease of regional cerebral activity in precuneus, the FC analysis showed increased connectivity between precuneus and brain regions including OFC and occipital lobe. This gave a more complete profile of the brain intrinsic functional changes referring to DMN. Decrease of connectivity between insula and cerebellum gave direct evidence of the involvement of central executive network (CEN)[3]. In summary, the above deficits in intrinsic brain function at resting state involving cerebellum, striatum, precuneus and insula provide cerebral functional changes in this special group of schizophrenia patients. Further study with graph theory would help to provide brain connectome information on it.

Reference:1.Andreasen, N.C., et al., Biol Psychiatry, 2008. 2.Davidson, R.J., Science, 2000. 3.Moran, L.V., et al., Biol Psychiatry 2013.