



F-18 fluorodeoxyglucose positron emission tomography study of impaired emotion processing in first episode schizophrenia

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ABSTRACT

Background: Schizophrenia cases have been consistently shown to have behavioural and neurofunctional abnormalities but studies during early course are scarce. The present work assesses the performance of acute first episode schizophrenia cases on correlation of a facial emotion perception task with brain function using fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET).

Methods: Twenty First episode schizophrenia cases and 20 matched healthy controls living in the community were enrolled. For cases, longest duration of illness was one year and treatment with neuroleptic did not exceed two weeks on the day of scan. To measure facial emotion perception (FEP) both groups were administered the Emotion battery from the Penn Computerized Battery followed by PET acquisition. SPM 8 analysis for group differences at $p < 0.001$ was performed.

Results: Schizophrenia subjects showed hypoactivation of bilateral prefrontal cortices and fusiform gyri, with significant hyperactivation of bilateral basal ganglia and left precuneus. Positive correlation of metabolism in prefrontal cortex and performance indices on emotions domain was seen. No correlation of chlorpromazine equivalent days with metabolism in basal ganglia was observed.

Conclusions: The performance of schizophrenia cases on FEP task was significantly impaired in comparison to the control group. Brain regions implicated in emotion processing showed hypometabolism in cases as compared to controls. Failure of schizophrenia cases to optimally recruit brain circuitry may be contributing to deficits on FEP task. These findings suggest inherent deficits in neural circuitry of emotion processing in schizophrenia; devoid of confounding effects of neuroleptics and duration of illness.

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1. Introduction

Neurocognitive impairment in schizophrenia is clinically relevant and profound. Schizophrenia cases perform worse than healthy controls on various neurocognitive tests including social cognition (Andreasen et al., 2008; Heinrichs and Zakzanis, 2001). There is growing evidence that social perception is related to social impairments and functional outcomes in schizophrenia (Nuechterlein et al., 2004; Dodell-Feder et al., 2014). Individuals with schizophrenia perform worse than healthy controls on tests of facial affect perception (Comparelli et al., 2013; Hempel et al., 2003). Deficits are observed early and remain over the course of illness (Comparelli et al., 2013; Kohler, 2010).

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In vivo brain F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a minimally invasive diagnostic imaging procedure used to evaluate cerebral glucose metabolism, a surrogate marker for neuronal activity. FDG-PET has been applied to facial emotion recognition (FER) studies to assess amygdalar activation and effects on other major emotion recognition related brain areas. In healthy subjects facial emotion perception results in activation of a circuit that includes the limbic system, fusiform gyrus, prefrontal cortices, anterior cingulate cortices and thalamus (Murphy et al., 2003; Addington et al., 2006; Sabatinelli et al., 2011). Hypoactivation of these brain regions in schizophrenia cases has been reported (Phan et al., 2002; Fernandez-Egea et al., 2010; Shin et al., 2014).

To our knowledge this is the first FDG-PET study to assess the whole brain circuitry involved in emotion processing in acute first episode schizophrenia as compared to healthy controls using a previously validated facial emotion perception (FEP) task, while minimizing

confounding factors like duration of illness (range 1 month to 1 year) and medication effects (maximum 2 weeks medication on day of scan). The same task was administered to both groups unlike in previous studies (Fernandez-Egea et al., 2010; Villalta-Gil et al., 2013) so that comparison of performance indices was not biased. Whole brain analysis was used so as to not limit the scope of identifying the neural circuitry involved in facial emotion perception in totality. Correlation with performance indices was performed.

2. Methods

2.1. Participants

Twenty one subjects, diagnosed as schizophrenia according to 10th revision of International Statistical Classification of Diseases (ICD-10 DCR) (World Health Organization, 1993), consulting the Psychiatry and De-addiction facility of a tertiary care teaching free hospital were enrolled. All subjects were between 18 and 50 years of age, male or female with duration of illness not exceeding one year. All were antipsychotic naïve at enrollment. Based on clinical judgment any one antipsychotic was started on enrollment. Anticholinergics were avoided. The time difference between enrollment and day of PET study was a maximum of 2 weeks. In addition 20 healthy individuals from the community between 22 and 35 years of age, male or female were recruited. Participants with current or past history of any major psychiatric disorder including substance abuse, co-morbid severe medical or neurological conditions were excluded. Healthy individuals with history of psychiatric illness in their first degree relatives were excluded. Pregnant females or lactating mothers were not recruited. The study was approved by the Institutional Ethics Committee, PGIMER-RMLH and written informed consent was taken from each individual included in the study.

2.2. Clinical assessment

All participants were right handed except one in control group. Diagnostic interview for genetic studies (DIGS)-Hindi version (Deshpande et al., 1998) was administered to the subjects for exploration of psychopathology and ruling out other psychiatric illnesses including substance use. The information obtained on DIGS was discussed with board certified psychiatrists and psychologists to establish consensus diagnosis. Positive and Negative Syndrome Scale was administered to the cases on the day of the PET scan (Kay et al., 1987).

2.3. Facial emotion perception (FEP) task

The task used was Emotion Recognition battery from Computerized Neurocognitive Battery (Penn CNP) (Gur et al., 2001). Developed at the University of Pennsylvania, this is a validated battery. It contains emotion recognition, discrimination and acuity tests, in addition to the face memory and motor praxis tests.

The Face Memory Test presents black and white 20 digitized faces intermixed with 20 distracters equated for age, gender and ethnicity. Subjects indicate whether or not they recognize each face immediately in multiple choice formats. Median time for the test is ~4.7 min. To use the task as a face identification test, we didn't ask our subjects to memorize faces.

Emotion Recognition includes facial displays of 40 coloured emotional stimuli. The faces consist of eight displays of each emotion (happy, sad, anger, fear, no emotion) arranged randomly. Subject identifies the emotion in a multiple-choice format.

Emotion Discrimination requires selection of more intense expression according to the question asked. Each stimulus presents two faces of the same individual showing the same emotion (happy or sad) with different intensities. There are 40 such pairs.

Emotional acuity includes facial displays of happy, sad or neutral emotions. Subject identifies the neutral faces and mild, moderate or severe intensity of happy and sad faces in a multiple choice format.

There was single trial for each test. The entire battery was completed in single sitting.

2.4. Administration of task and data acquisition

The FEP task and the FDG-PET study were conducted at the PET Facility in the Institute of Nuclear Medicine and Allied Sciences. Subjects sat on a comfortable chair in front of the laptop screen 15" in dimension and were provided with an optical mouse. Peripheral intravenous access was secured after checking random blood sugar level. The subjects who had not worked on computer were instructed as to how to use the mouse. Un-speeded version of motor praxis test was completed by all subjects. 222–296 MBq of 18F-FDG was administered 5 min after the face identification test was initiated. The test was administered using clickable icons on desktop in a pre-fixed order and time. All four tests began with a practice module, to ensure understanding instructions. The cases took 30–45 min (average: 37.6 min) to complete the task while controls took 17–30 min (average: 26.3 min). Subjects were made to sit in a comfortable quiet and dimly lit room after the task was completed. Each subject was then positioned supine on the PET/CT scanner, Discovery STE16 (General Electric Medical Systems, Milwaukee, WI, USA) 45 min after tracer administration. Head was positioned in a head holder, and an initial scout was followed by low dose (110 mA, 120 kVp) CT. Then a single bed position 3D emission PET scan was acquired for 20 min. CT was used for attenuation correction of PET images. One case did not co-operate for the task and was excluded. Three schizophrenia subjects were unable to lie still in the scanner. Injection midazolam was administered to them after 45 min or more of injecting the dye. As it was injected after 45 min of FDG, the possibility of altering metabolism is minimal.

2.5. Image processing and analyses

2.5.1. Pre-processing

Data were first preprocessed, realigned, normalized to the Talairach and Tournoux atlas space, registered to a template with affine and non-linear transformation and smoothed using an isotropic 10 mm full-width at half-maximum Gaussian kernel. Statistical Parametric mapping version 8 (SPM-8) (www.fil.ion.ucl.ac.uk/spm/) implemented on a MATLAB (Mathworks, Inc) platform was used for voxel based statistical analysis of images, which combines the general linear model with the theory of Gaussian fields to make statistical inferences about regional effects.

2.5.2. First-level analysis

Both groups were compared using a two-sample *t*-test. The measurements were assumed to be independent and to have unequal variance between levels. Age, gender and education were included as regressors of no interest. It essentially compares regional differences in relative glucose metabolism. Statistical threshold was fixed at $p < 0.001$ (uncorrected) with no minimum-activated voxel threshold.

2.5.3. Second-level analysis

Correlation analyses were carried out using ANCOVA. Age, sex and years of education were included as nuisance covariates while each performance index and chlorpromazine equivalent days were covariates of interest. Statistical threshold was fixed at $p < 0.001$ (uncorrected) with no minimum-activated voxel threshold.

Proportional scaling to the global mean was used to minimize inter-subject variability. Proportional scaling basically scales each image according to a reference count, which is the global brain activity to a physiologically realistic value of 50 ml/dl/min. The statistical 't' maps thus obtained were overlaid onto the T1-weighted MRI template

image provided by SPM8. At the end the SPM.mat file containing the specified design matrix was generated. Using this file contrasts were defined providing a map of voxels. The results were co-related using the Automated Anatomical Labeling (AAL) Tool Box and Montreal Neurological Institute (MNI) co-ordinates for each of the significant cluster was localized and the corresponding brain region was identified.

2.6. FEP performance score analysis

The data from Emotion Recognition, Emotion Acuity and Emotion Discrimination were clubbed into Emotions domain while Data from Immediate Face Memory task was presented in the domain of Face Memory. Raw scores were converted to z scores using the comparison group mean and then averaged to obtain domain scores. For each of the domains three performance indices were calculated: a) accuracy—number of correct responses, b) speed—median reaction time for correct responses and c) efficiency—reflects both accuracy and speed (accuracy/log of speed). The method used is a standard way of analyzing the data from this battery described by its authors (Gur et al., 2001). For the analysis of categorical and continuous variables Chi-square test and Mann Whitney Wilcoxon sum rank test respectively, were used. Linear regression was applied separately for each performance index in both domains to correct for age, gender and education. The Statistical Package for Social Sciences (SPSS), version 17.0 was used.

3. Results

3.1. Clinical and behavioural data

The final sample included 20 in each group (Table 1). All subjects self identified themselves as right handed except for one control. Mean scores on PANSS suggested moderate severity of illness. Participants were either on olanzapine ($n = 11$, 10–20 mg), risperidone ($n = 6$, 2–6 mg), haloperidol ($n = 2$, 20 mg) and one was drug naïve. Treatment duration varied from 10 to 14 days for 9 cases, 6 to 8 days for 8 cases and ≤ 3 days for 2. For chlorpromazine equivalent days, average was 2645 ± 1721.53 (Table 1). The performance of cases was worse than the controls on FEP task. Irrespective of age, gender, education; their health status was the most important factor for poor task performance (Table 2).

3.2. FDG-PET data

Analysis at $p < 0.05$ showed hypoactivation of bilateral prefrontal cortices (left > right), orbitofrontal cortices, anterior cingulate cortex, fusiform gyrus, parahippocampal gyri (PHG), thalamus, occipital cortex, left motor cortex and right cerebellum in schizophrenia subjects as compared to the control group. Cases also showed hyperactivation in bilateral putamen (right > left) and left precuneus. Analysis at

$p < 0.001$ (uncorrected) revealed hypoactivation of bilateral dorsolateral prefrontal cortices and fusiform gyri in cases compared to controls. Hyperactivation in bilateral basal ganglia and left precuneus was also observed. Table 3 enumerates the most significant foci for each brain region showing differential activation ($p < 0.001$).

3.3. Correlation analysis

Metabolism in prefrontal cortex was positively correlated to performance indices on emotions domain. There was no correlation between CPZ equivalent days and metabolism in basal ganglia.

4. Discussion

To our knowledge this is the only report of neural correlates of facial emotion processing in acute first episode schizophrenia as compared to controls at the whole brain level. We used a uniform protocol to ensure a homogenous sample so as to maximize the chances of true findings in a field of research where confounding factors lead to much uncertainty.

4.1. Sample characteristics

The cases and control group were matched for age, gender, education and handedness as various authors have indicated that these factors may affect the performance as well as differential activation of brain regions (Solodkin et al., 2001; Kawachi et al., 2002; Pardo et al., 2007; Williams et al., 2009; Helmich et al., 2013; Kaneda et al., 2013). Maximum duration of treatment was limited to two weeks to control for changes in activation pattern in different brain regions due to neuroleptics (DeLisi et al., 1985; Lui et al., 2010).

4.2. Facial emotion task

Though the study group fared poorly as compared to control group on all indices; their speed of performance was worst affected, thus indicating that overall reaction time is markedly increased in schizophrenia even when they reach the right answers. This slowness in reaching answers obviously affects daily life in persons with schizophrenia. The impaired performance of schizophrenia cases on both face memory and emotions domain were similar to other reports (Green et al., 2009; Kohler et al., 2010; Chen et al., 2012; Comporelli et al., 2013).

4.3. PET findings

As compared to controls persons with schizophrenia showed hypometabolism of bilateral dorsolateral prefrontal cortex and fusiform gyri with hyperactivation of bilateral basal ganglia and left precuneus.

The hypoactivation observed in fusiform gyri was similar to other studies (Li et al., 2010; Sugranyes et al., 2011). Fusiform gyrus is especially activated by the sight of faces (Taylor et al., 2012). Thus the hypoactivation of fusiform gyrus suggests impairment in processing of perceived visual stimuli in schizophrenia (Seiferth et al., 2009; Lepage et al., 2011).

There was significant hypoactivation of bilateral prefrontal cortices in schizophrenia cases as compared to the controls (Brunet-Gouet and Decety, 2006; Taylor et al., 2012). The hypometabolism in pre-frontal cortex in schizophrenia points to disruption in the integrated cognitive and emotional network and markedly reduced recruitment of the brain areas involved in processing of emotion in schizophrenia (Sugranyes et al., 2011; Shin et al., 2014; Tully et al., 2014). Left hemisphere being the dominant hemisphere and implicated in cognitive processing as compared to right showed greater hypoactivation than the right, as in earlier studies (Russell et al., 2000).

Amygdala shows the greatest activation during FER task (Fernandez-Egea et al., 2010). Our study did not find any significant difference in metabolism between the cases and control group in this

Table 1
Demographic and clinical data.

	Study group N = 20	Control group N = 20	χ^2 (chi-square) value	p-Value
Age (in years)	29.0 \pm 8.6	28.1 \pm 3.5	0.136	0.892
Gender (M:F)	12:8	13:7	0.107	0.744
Education (in years)	8.8 \pm 5.0	8.9 \pm 4.1	0.136	0.892
Duration of illness (in weeks)	20.1 \pm 14.8			
Duration of treatment (in days)	8.4 \pm 5.2			
CPZ equivalent days	2645 \pm 1721.53			
Positive PANSS score	19.8 \pm 4.1			
Negative PANSS score	16.3 \pm 5.2			
General PANSS score	34.3 \pm 3.7			
Total PANSS score	70.4 \pm 8.4			

Note: CPZ = Chlorpromazine, PANSS = Positive and Negative Syndrome Scale.

Table 2

Comparison of emotion recognition battery domain indices in study and control group.

Dependent variables (performance indices)	Significant independent variables	Standardized coefficient beta (B)	p Value	95% confidence interval for B
Face memory accuracy	Health status	0.376	0.017	0.222,2.097
Face memory speed	Gender	−0.278	0.033	−4.247, −0.184
	Health status	0.566	<0.0001	2.398,6.332
Face memory efficiency	Health status	0.505	0.001	0.8,2.681
Emotion accuracy	Health status	0.39	0.01	0.174,1.221
Emotion speed	Health status	0.696	<0.0001	1.376,2.713
Emotion efficiency	Health status	0.511	<0.0001	0.538,1.713

region as others (Reske et al., 2009; Ursu et al., 2011), perhaps because tasks requiring greater cognitive demand are less likely to activate amygdala than those requiring only passive viewing (Satterthwaite et al., 2010; Pinkham et al., 2011). A whole brain analysis as compared to region of interest analysis and studies using PET as compared to functional magnetic resonance imaging (fMRI) are less likely to detect amygdalar activation (Costafreda et al., 2008). Thus there is a possibility that this finding may be due to low power to detect amygdala activity, rather than as a result of a true absence of differential activity.

There was significant hyperactivation in bilateral basal ganglia especially putamen in the study group when compared to controls. Other studies report that it may be due to medication effect (Buchsbaum et al., 1987; Lui et al., 2010). No correlation of CPZ equivalent days with metabolism in basal ganglia suggests an alternate mechanism unrelated to drug effect (Reske et al., 2007; Ursu et al., 2011). Basal ganglia consist primarily of inhibitory projections from prefrontal cortex and are involved in inhibition of inappropriate behavior and guiding towards a desired goal (Ruppin et al., 1999; Gangadhar et al., 2004). Thus it can be hypothesized that the hyper-metabolism in basal ganglia seen in our study could be due to impaired activity of the frontostriatal pathways.

There was also hyperactivation in left precuneus in the case as compared to the control group (Fakra et al., 2008; Reske et al., 2009). Increased activity in this region might be a compensatory process to overcome deficits due to hypoactivation in other regions involved in emotion processing (Seiferth et al., 2009; Taylor et al., 2012).

Thus brain regions implicated in emotion processing showed hypometabolism (surrogate marker for neuronal dysfunction) in schizophrenia cases as compared to controls. Positive correlation of metabolism in prefrontal cortex and performance indices on emotions domain implies that dysfunctional brain metabolism in schizophrenia may be the basis of impaired performance on emotion task. Other authors have also arrived at this conclusion (Russell et al., 2000; Sugranyes et al., 2011; Taylor et al., 2012).

4.4. Conclusion and limitations

The performance of schizophrenia cases on FEP task was significantly impaired in comparison to the control group. Neuronal circuitry implicated in emotion processing and overall performance of the FEP

task showed evidence of dysfunction. These findings were devoid of confounding effects of neuroleptics and duration of illness. Metabolism in prefrontal cortex was positively correlated with performance on emotions task. Thus one can conclude that failure of schizophrenia cases to optimally recruit the brain circuitry may be contributing to deficits on FEP task.

Although sample size was small, the numbers were comparable to other similar studies. Numbers of female participants were low in both groups. The groups were statistically similar but not matched one to one. One subject was left handed; although results were not significantly skewed due to this, corrections may need to be made in future studies. As the task was done outside the scanner, the rest time for each subject before the actual scan differed. There is possibility of different time for rest introducing confound. A control task would have resulted in better understanding of underlying neural network. Further research is required to understand the role of changes in brain activity and their influence on social functioning of schizophrenia cases. Future studies may help in establishing targets for treatment interventions.

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Contributors

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Conflict of interest

There is no conflict of interest to be declared by any of the authors.

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Table 3

Maxima of significant differences b/w study & control group in regional brain activation.

Anatomical region	MNI coordinates			Significance	
	X	Y	Z	T	p Value
<i>Regional cerebral blood flow lesser in study group in comparison to controls</i>					
Right dorsolateral prefrontal cortex	54	26	34	5.35	<0.001
Left dorsolateral prefrontal cortex	−24	30	44	5.22	<0.001
Right fusiform gyrus	62	−40	−18	3.75	<0.001
Left fusiform gyrus	−64	−38	−12	4.04	<0.001
<i>Regional Cerebral Blood Flow Greater In Study Group In Comparison To Controls</i>					
Right putamen	30	22	28	4.75	<0.001
Left putamen	−28	−30	44	4.15	<0.001
Left precuneus	−12	−60	32	3.73	<0.001

Note: MNI = Montreal Neurological Institute, T = Height Threshold.

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