Differentiating Schizophrenia from Bipolar Illness on 18 F FDG PET CT Based on white Matter Metabolism; an under-Utilised Parameter

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Abstract: 18F-FDG PET/CT positron emission tomography studies (FDG-PET) have shown similar cortico-limbic metabolic dysregulation in bipolar disorder and schizophrenia, with hypoactive prefrontal cortex coupled with hyperactive anterior limbic areas. However, it is not clear whether white matter metabolism connecting these regions is differently affected in the two disorders. Forty eight patients with schizophrenia mean age ± S.D] 31.6 ± 7.8 and 56 patients with bipolar disorder [mean age±S.D] 46.2 ± 8.9 underwent an 18F-FDG PET/CT scan. Normalized datasets the two groups of patients were compared on a voxel-by-voxel basis using a two-sample t statistic test as implemented in SPM8, and adding age as covariate. Group differences were assessed applying a threshold of $p<0.0005$. White matter metabolic rates significantly differed between schizophrenia and bipolar disorder, whereas no differences were shown for cortical activity. This is the first 18F-FDG PET/CT to our best knowledge, directly comparing subjects with schizophrenia to those with bipolar disorder. It reports decreased activity in the center of large fronto-temporal and cerebellar white matter tracts in patients with schizophrenia in respect to those with bipolar disorder. This feature may characterize and differentiate the regional brain metabolism of the two illnesses.

Keywords: Schizophrenia, Bipolar illness, Mania, Depression, White matter, Cortical, Brain, Imaging, 18F-FDG PET/CT.

1. INTRODUCTION

Functional neuro imaging studies with F-18 fluoro-deoxyglucose based Positron emission tomography(FDG-PET) have demonstrated a possible cortico-limbic metabolic dysregulation in bipolar disorder with features of hypermetabolism involving the limbic regions (anterior temporal cortex, parahippocampal gyrus,cingulate region and amygdala) accompanied by hypometabolism in the prefrontal cortex (*i.e.*, dorsolateral prefrontal cortex (DLPFC) and anterior cingulate) [1]. The glucose metabolism has been correlated with cognitive, attention and memory deficits in such patients with manic -depressive phases;even during euthymic phases [2, 3].A recent meta analyses on functional neuro imaging studies with a large volume of patients with bipolar disorder and normal controls, also confirmed a possible underlying anterior paralimbic dysregulation [4]. However, multiple studies on functional neuro imaging in schizophrenic patients have also demonstrated prefrontal and anterior cingulate hypo-metabolism [5-11]. In addition, posterior limbic, amygdalar, basal ganglial, and temporal hyper metabolism has been observed in schizophrenia [9, 12]. Similar findings of temporal lobe hyper perfusion and cortical hypoperfusion have been described in functional and contrast enhanced MRI in bipolar [13] and schizophrenic patients. [14] Thus it becomes difficult to differentiate between the two conditions based on FDG PET as a similar prefronto-limbic dysregulation might characterize the two disorders. A progressive decrease in pre-frontal activity in schizophrenia and bipolar disorder could result in a loss of inhibition or modulatory control over the deeper limbic structures, which would as a corollary show increased activation [15]. As there is an overlap of clinical features between the two conditions, it would be illuminative to identify contributory imaging features to differentiate between schizophrenia and bipolar illness. Studies have revealed widespread abnormalities characterized by a lower fractional anisotropy neuroanatomically associated with localized reduced grey matter in the schizophrenic group. The grey matter changes can either be interpreted as the result of a locally reduced cortical thickness or as a manifestation of different patterns of gyrification. There was a widespread reduction of anisotropy in the white matter, especially in the corpus callosum. It is speculated that the anisotropy changes relate to the functional changes in brain connectivity that are thought to play a central role in the clinical expression of the disease. The distribution of grey matter changes are usually consistent with clinical features of the

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disease. The metabolic rates of white matter connections between the (hypo-active) prefrontal regions and the (hyperactive) limbic structures and their potential role in specific diseases have not been delineated yet. Only two prior PET studies have hypothesized and investigated altered fronto-limbic connectivity based on altered anterior–posterior metabolism in both schizophrenia and bipolar disorder [16, 17].

In this study we compared brain metabolism with 18F-FDG PET/CT in a sizeable population composed by either schizophrenia or bipolar disorder patients in order to directly compare cortical and white matter metabolism characterizing the two disorders.

2. METHODS

2.1. Subjects

Forty-eight patients with schizophrenia and 56 patients with bipolar disorder, who were referred for

F-18 FDG PET CT of the brain was included in the study. Demographic data as well as other disease related parameters are given in Table **1**.The study was cleared by the Institutional review board and written informed consent was obtained from all the patients. In patients who were considered incompetent to give consent, the same was obtained from their spouse, parents or immediate relative who was responsible for the patients care.

Inclusion criteria were as follows: current diagnosis of schizophrenia and bipolar disorder according to the DSM-IV-TR diagnostic criteria [American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®. American Psychiatric]

And duration of untreated illness not longer than 5 years. Diagnoses were made using SCID for DSM-IV-TR Axis I; interviews were conducted by raters with extensive experience in administering the SCID. Majority of the schizophrenia patients were experiencing acute psychosis (14 during their first episode), whereas bipolar disorder patients were suffering different mood episodes (32 depressed, 9 manic, and 15 mixed episodes) when referred. However, patients were studied with PET when they were relatively clinically stable. Patients with schizophrenia, were scored with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and had a score of less than 50 at the time of scan. Similarly, for those with bipolar disorder, the Hamilton

Table 1: Patient Characteristics

Patients Features	Patients with Schizophrenia (n = 48)	Patients with Bipolar Illness (n = 56)	Significance + if p < 0.01 - if p >0.05 ± if 0.01<p >0.05
Mean age ± SD(years)	31.6 ± 7.8	46.2 ± 8.9	+
Sex (male/ female)	32/16	32/24	-
Age of onset± SD(years)	24.6 ± 4.1	34 ± 6.7	+
Duration of illness ± SD(years)	6.8 ± 3.1	12 ± 8.1	-
Number of hospitalizations	3.1 ± 2.2	2.9 ± 3.5	-

Table 1: Calculated Metabolic Ratios and Standard Deviations

	Patient group		Control Group	
	Mean SD		Mean SD	
Frontal/occipital	1.1	0.09	1.02	0.05
Parietal/occipital	1.07	0.06	1.05	0.05
Temporal/occipital	0.96	0.05	0.91	0.03
Thalamus/occipital	0.97	0.04	0.92	0.06
Striatum/occipital	1.14	0.08	1.08	0.05

Depression Rating Scale (HDRS) scores and the Young Mania Rating Scale (YMRS) scores had to be <8 and <10, respectively. All patients were on treatment, *i.e*., those with schizophrenia were on antipsychotics and benzodiazepines and those with bipolar disorder were on antipsychotics, mood stabilizers, benzodiazepines, and/or antidepressants

Exclusion criteria included a diagnosis of mental retardation, any lifetime history of significant medical or neurological illnesses and substance abuse disorder. Information concerning socio-demographic variables were collected from patients or from their parents/relatives.

2.2. PET Scan

18F FDG was obtained from a commercial supplier after passing the necessary quality control, sterility and other parametric testing as mandated internationally. The cyclotron was a GE model 16 Mev cyclotron. It was obtained in a ready to use formulation, dispensed with individual patient doses under sterile and apyrogenic condition.

FDG-PET scanning was performed on a Siemens Symbia 6 PET CT scanner. The scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of the axial field of view. Data acquisition follows a standardized protocol established at the Department of nuclear medicine at the Kovai Medical Centre and Hospital. An intra venous injection of 170 MBq (F-18) FDG was given to each patient after overnight fasting and checking of fasting blood sugar levels. This is followed by an uptake period of 30 to 45 minutes during which time patient is placed in a dark room with no visual or auditory stimuli and encouraged to relax. Each patient is then scanned with eyes closed in a moderately light environment. The head of the patient is fixed in a head holder and adequately positioned in the gantry. Acquisition starts with a diagnostic CT transmission scan used for subsequent attenuation correction. This is followed by the emission scan (3 frames, 10 minutes/ frame, 128 x 128 matrix, 3D acquisition). Images were reconstructed by iterative reconstruction using OSEM. Images were corrected for scatter and attenuation.

2.3. PET Analysis

As first step of the PET image analysis, standardized uptake value (SUV-a semi quantitative index of the fractional uptake rate of [18F] FDG) maps have been derived from the original [18F] FDG images by using the following formula:

$$SUV = \frac{AC}{(FDGdose/\ BW)}$$

Where AC is the activity of -tracer concentration in a given voxel [kBq/ml], FDG dose is the injected radio-tracer dose corrected for residual activity in the syringe [MBq], and BW is the body weight [kg]. All the radio-tracer data were decay corrected before their use.

The data obtained from the reconstructed PET images was transferred to a work station with Scenium software (Siemens) which enables one to compare the patient data after stereotactic realignment to a 3-dimensional reference template created from a normal database of 102 patients. Deviations from the normal database may be assessed on the voxel-level evaluating statistical differences using the standard deviation criterion. This approach allows one to compare the baseline status in different individuals with a normal database as well as to assess the intrasubject variation in repetitive studies on the same individual. Data from the set of 63 ROIs covering the whole brain were pooled and combined to separate ROIs for frontal, parietal, temporal, occipital cortex as well as striatum, thalamus, cerebellum and brainstem.

Performing a t-test, the ages of the two groups are not statistically different ($p > 0.05$). Several additional combinations of covariates were used including age at onset, mood state, number of hospitalizations, PANSS, HDRS, and YMRS scores, type of medication, drug dosages, but none had any significant impact on the results.

Statistics

All statistics have been calculated using the SPSS software package. Ratios between different regions and the occipital cortex have been calculated to compensate for inter-individual variation of metabolic rates. Mean and standard deviation values have been calculated for the ratios to describe the distribution of the data. Student t tests were used to compare group differences between the patient group and the control group.

3. RESULTS

Regional Metabolic Rates of Glucose

Metabolic activity corrected for the time of administration of 18 FDG was calculated for both

patients with schizophrenia and with bipolar disorder and compared with the normal population.

Compared to the normal database population, both patient groups demonstrated pre frontal hypometabolism with increased hippocampal, amygdalar and cingulate metabolism. Patients in acute psychosis did demonstrate an associated increased dorso-lateral frontal and parietal metabolism while subjects with depression demonstrated associated basal ganglial and thalamic hypermetabolic pattern; though there was no statistically significant association noted. Since the standard deviation of the SUV's were high in both groups and in all examined regions indicating a high inter-individual variation, more attention was paid to ratios between brain regions and the occipital cortex as reference, referred to as 'metabolic ratios'. These also play an important role in diagnosing cortical and white matter hypo- or hyper-metabolic pattern. Table **2** gives an overview of the calculated ratios as well as their standard deviation and also illustrates differences between the patient groups.

The mean frontal-occipital, parietal- occipital, anterior limbic- occipital, thalamus- occipital, tempero-occipital and striatum- occipital ratio in both groups of patients did not show any statistically significant difference. Among all examined metabolic ratios the ratios showing the strongest difference between the 2 patient groups were the Fronto temporal/tempero-parietal and cerebellar white matter – occipital ratios. Looking at the two hemispheres separately revealed all together more significantly different metabolic ratios between patients and controls in the right hemisphere than on the left side. To compare the examined cortex areas directly between the two hemispheres, we calculated additional right to left ratios for each region, which did not show any statistically significant different patterns between patients' and control studies (Table **2**).

White matter metabolism differed in patients with schizophrenia in comparison to those with bipolar disorder ($p < 0.0005$), particularly in major frontal, parietal, and temporal tracts, as well as in pons and cerebellum, even after covarying for medication load. In these areas the tracer metabolism of the subjects with bipolar disorder was higher than those of patients with schizophrenia. In contrast, in our population, there were no significant differences in cortical tracer metabolism in individuals with schizophrenia or bipolar disorder.

4. DISCUSSION

Our study is an initial attempt to directly compare the resting regional metabolism of schizophrenia to that of bipolar disorder and it shows decreased activity in the white matter tracts predominantly in the fronto-temporal, tempero-parietal and cerebellar regions in patients with schizophrenia. We could not find any statistically significant difference in the cortical

Table 2: Calculated Metabolic Ratios and Standard Deviations

	Schizophrenia Group		Bipolar illness Group	
	Mean SD		Mean SD	
Frontal/occipital	0.5	0.09	0.4	0.05
Parietal/occipital	1.07	0.06	1.05	0.05
Anterior limbic/occipital	1.3	0.04	1.2	0.02
Temporal/occipital	0.96	0.05	0.91	0.03
Thalamus/occipital	1.08	0.04	1.14	0.06
Striatum/occipital	1.01	0.08	1.08	0.05
FT WM/occipital	0.4	0.03	0.97	0.1
TO WM /occipital	0.5	0.05	1.01	0.08
Cerebellar WM/occipital	0.3	0.04	0.95	0.06

FT: Fronto- temporal, TP: Tempero – parietal, WM: white matter

metabolic patterns between the two patient groups, which is in conformity with multiple earlier reports, and PET literature which were summarized earlier.

A previous study has reported altered and reduced white matter metabolic rates in schizophrenia [18] and another study by Altamura et.al has suggested significant difference between schizophrenic and bipolar subjects with regards to white matter metabolic rates [17]. Our study demonstrates a similar picture of consistent, confluent hypometabolism involving large white matter tracts, more pronounced in schizophrenia. Similarly a common finding of frontal hypometabolism with relative sparing or hypermetabolism of posterior cingulate region in both schizophrenia and bipolar illnesses are also similar to previous studies.

Multiple MRI studies have also demonstrated abnormalities in brain connectivity, shown by increased rates of white matter hyperintensities, regional structural alterations and water diffusion impairments, in both disorders [19-23]. The most commonly reported impairments have been in the frontal and temporo-parietal longitudinal and inter-hemispheric tracts [24-27] along with cerebellum and pons [28-32]. It is interesting to note that , such white matter impairments appear to be more severe and generalized in schizophrenia in respect to bipolar disorder [33, 34], with more pertinent links to genetics and molecular infiltrates.[35, 36]. Consequently it is possible that the variance in white matter metabolism observed in the two disorders could be due to underlying distinctive structural connectivity alterations. Our study contributes significant functional and metabolic correlation to the premise that fronto-limbic and cerebellar white matter activity may be differentially affected in schizophrenia and bipolar disorder, and FDG PET could serve in characterizing the two illnesses. Thus, the finding of similar cortical metabolic pattern in the two disorders could also strengthen the ongoing debate concerning the Kraepelinian dichotomy of the two illnesses [37].

Hypotheses concerning the changes in white matter function, structure and metabolism deal propose underlying deficits in neuronal circuits, accelerated and increased tissue damage, impaired axon laying and packing density as well as neuro chemical alterations. Post mortem studies in schizophrenia and bipolar disorder have demonstrated at the microscopic level, lowered density of oligodendroglial cells due to apoptosis and necrosis, particularly in the pre-frontal cortex and cingulate white matter contributing to underlying cortico-limbic disconnectivity [38, 39]. Oligodendrocytes have been reported to have a trophic influence on neurons and thus, could play a key role in inducing altered neuronal connectivity and atrophy in these disorders [40]. Moreover genetic defects contributing to deficits in the expression of oligodendrocyte and myelin have been observed in both schizophrenia and bipolar disorder [41, 42], potentially explaining the presence of fewer oligodendrocytes. As glucose is crucial for sustaining neuron–glia interaction and synaptic plasticity, such as for the GABAergic and glutamatergic systems, glucose consumption and 18FDG uptake analysis could be considered as an indirect and associated marker of neural tract integrity. Summarizing these findings, altered white matter metabolism may play a crucial role for the patho-physiology of these disorders, potentially accompanying the above mentioned alterations of oligodendrocyte viability [43, 44].

Conclusion: Our study suggests that altered white matter activity might serve as a potential biomarker helping in separating schizophrenia and bipolar disorder. Functional and neuro imaging features , exploring similarities and differences in cortical and sub cortical metabolic patterns can lead the way forward in further understanding the complex etio-pathogenesis of these two disorders and can also correlate with their phenotype expression [43, 45]. Such similarities in cortical metabolism patterns could renew the interest of the clinicians regarding the validity of the hypothesis that schizophrenia and bipolar disorder can be conceptualized as a continuous spectrum of clinical phenotypes rather than as distinct categories, in the context of the Kraepelinian dichotomy [46, 47].

Larger PET studies should be undertaken to elucidate metabolic changes in schizophrenia and bipolar disorders, especially in drug naive subjects at their very first consultation if possible, to avoid the potential influences of chronicity and medications, and compare with age- and gender-matched control individuals.

LIMITATIONS O F THE STUDY

A significant drawback of the study was that all the patients were on regular psychiatric and drug treatment. Thus it is difficult to rule out the effects of psychotropics. Some of the patients were on combination therapy and multiple studies have described the underlying functional changes in brain metabolism after drug therapy. Thus it is difficult to separate out the effects of medication from disease patho-physiology in such patients

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