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White matter metabolism differentiates schizophrenia and bipolar disorder: a preliminary PET study

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ABSTRACT

Fluorodeoxyglucose-F18 positron emission tomography studies (FDG-PET) have shown similar corticolimbic 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. Twenty-six patients with schizophrenia (mean age ± S.D. = 30.23 ± 9.7 year-old; 19 males; mean weight ± S.D. = 71 ± 3 kg) and 26 patients with bipolar disorder (mean age ± S.D. = 48.73 ± 13 year-old; 18 males; mean weight ± S.D. = 75 ± 15 kg) underwent an FDG-PET 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 FDG-PET, 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.

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1. Introduction

Positron emission tomography studies using fluorodeoxyglucose-F18 (FDG-PET) have pointed out in bipolar disorder the potential presence of a corticolimbic metabolic dysregulation at rest, involving excessive anterior limbic metabolic rates (anterior temporal cortex, parahippocampal gyrus, and amygdala) accompanied by diminished prefrontal activity (i.e., dorsolateral prefrontal cortex, DLPFC, and anterior cingulate) (Brooks III et al., 2009a), which also correlated to cognitive deficits, such as impaired sustained attention and verbal memory, even during euthymia (Brooks III et al., 2009b, 2010). This anterior paralimbic dysregulation has recently been confirmed by a meta-analysis conducted on functional neuroimaging studies including 774 adult patients with bipolar disorder and 810 healthy adult controls (Kupferschmidt and Zakzanis, 2011). In parallel, hypoactive (dorsomedial and dorsolateral) prefrontal and cingulate metabolism in patients diagnosed with schizophrenia has well been established by neuroimaging studies (Haznedar et al., 2004; Lehrer et al., 2005; Horacek et al., 2006; Park et al., 2006; Fujimoto et al., 2007), correlating in particular to processing speed (Molina et al., 2009) and anhedonia (Park et al., 2009). Also, limbic hyperactivation, including amygdala, basal ganglia, and temporal regions, has been observed in schizophrenia (Fujimoto et al. 2007; Fernandez-Egea et al., 2010). Such PET findings partially overlap with prior studies from our group where, utilizing dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI), hyperperfusion in temporal lobes was noted in bipolar disorder (Agarwal et al., 2008) and cortical hypoperfusion in schizophrenia (Peruzzo et al., 2011).

Therefore, based on the PET studies, a similar prefronto-limbic dysregulation might characterize the two disorders. In particular, since regional cerebral metabolic rate is often used as a surrogate measure

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of neuronal synaptic activity, the above mentioned decreased prefrontal activity in schizophrenia and bipolar disorder might reflect a loss of modulatory control over limbic structures, which would therefore present as hypermetabolic (Gonul et al., 2009). However, the metabolic rates of white matter connections between the (hypoactive) prefrontal regions and the (hyperactive) limbic structures have not been delineated yet. Only one prior small PET study hypothesized altered fronto-limbic connectivity based on altered anterior–posterior metabolism in both schizophrenia and bipolar disorder (al-Mousawi et al., 1996).

In this study we compared brain metabolism with FDG-PET in a sizeable population composed by either schizophrenia or bipolar disorder patients in order to directly compare, for the first time to the best of our knowledge, cortical and white matter metabolism characterizing the two disorders.

2. Methods

2.1. Subjects

Twenty-six patients with schizophrenia and 26 patients with bipolar disorder were recruited at the psychiatric inward of the University Policlinico Hospital of Milan, Italy (Table 1). Inclusion criteria were as follows: current diagnosis of schizophrenia and bipolar disorder according to the DSM-IV-TR diagnostic criteria, 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. Schizophrenia patients were experiencing acute psychosis (10 during their first episode), whereas bipolar disorder patients were suffering different mood episodes (13 depressed, 7 manic, and 6 mixed episodes) when admitted. However, patients were studied with PET when they were relatively clinically stable. Indeed, for patients with schizophrenia the scores at admission of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) had to decrease of at least 50%. Similarly, for those with bipolar disorder the Hamilton Depression Rating Scale (HDRS) scores and the Young Mania Rating Scale (YMRS) scores had to be <8 and <10, respectively. Participants were asked to provide a urine sample for toxicologic analysis to exclude a current substance use. 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 (Table 2). Only two patients with schizophrenia and one with bipolar disorder were on monotherapy (i.e., quetiapine 500 mg, olanzapine 20 mg, aripriprazole 15 mg, respectively).

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

2.2. PET scan

All patients underwent ^{18}F-fluoro-2-deoxyglucose positron emission tomography scanning (FDG-PET) at rest, after intravenous injection of 170 MBq. They were positioned comfortably in a quiet, dimly lit room several minutes before FDG administration and during the uptake phase of FDG for at least 30 min and were instructed not to speak, read or be otherwise active. Each acquisition included a Computed Tomography (CT) transmission scan of the head (50 mA lasting 16 s) followed by a three-dimensional (3D) static emission of 15 min using a Biograph Truepoint 64 PET/CT scanner (Siemens, Erlagen, Germany). PET sections were reconstructed using an iterative algorithm (OS-EM), corrected for scatter and for attenuation using density coefficients derived from the low dose CT scan of the head obtained with the same scanner, with the proprietary software. Images were reconstructed in the form of transaxial images of 128×128 pixels of 2 mm, using an iterative algorithm, ordered-subset expectation maximization (OSEM). The resolution of the PET system was 4–5 mm FWHM.

Table 1
Patients' features.

	Patients with schizophrenia ($N=26$)	Patients with bipolar disorder ($N=26$)
Mean age ± S.D. (years)	30.23 ± 9.7	48.73 ± 13*
Males	19	18**
Weight ± S.D. (kg)	71 ± 3	75 ± 15**
Mean age of onset ± S.D. (years)	22.46 ± 6.03	31.04 ± 11.97*
Mean number of prior hospitalizations ± S.D.	2.88 ± 2.57	2.78 ± 4.17**

The two patient groups statistically differed for age and age at onset (*$p<0.01$) but not for the other variables (**$p>0.05$) (Student t-test).
S.D. = standard deviation.

Table 2
Patients' medications.

	Patients with schizophrenia Number (mean dosages, range)	Patients with bipolar disorder Number (mean dosages, range)
Antipsychotics		
Quetiapine	14 (398.21; 50–800)	15 (310; 100–600)
Olanzapine	14 (24.64; 10–40)	11 (25.25; 2.5–40)
Zuclopenthixol	13 (32.38; 10–60)	6 (30; 15–60)
Aripriprazole	8 (26.56; 20–30)	8 (19.38; 5–30)
Risperidone	7 (6.43; 4–9)	1 (3)
Paliperidone	7 (9; 6–12)	1 (12)
Haloperidol	6 (4.50; 2–9)	1 (1)
Ziprasidone	3 (160)	1 (60)
Clozapine	2 (150 e 250)	
Mood stabilizers		
Valproate		14 (1182; 600–2000)
Gabapentin		5 (840; 600–900)
Lithium		4 (750; 600–900)
Preagabalin		2 (75 e 135)
Topiramate		2 (150 e 600)
Lamotrigine		1 (75)
Antidepressants		
Venlafaxine		5 (150; 75–300)
Chlomipramine		2 (75 e 150)
Duloxetine		2 (60 e 90)
Benzodiazepines		
Clonazepam	13 (2.77; 1–6)	9 (2.94; 1–6)

2.3. PET analysis

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

$$SUV = \frac{AC}{[FDG_{dose}/BW]}$$

where AC is the activity radiotracer concentration in a given voxel [kBq/ml], FDG_{dose} is the injected radiotracer dose corrected for residual activity in the syringe [MBq], and BW is the body weight [kg]. All the radiotracer data were decay corrected before their use.

Subsequently, the SUV images have been spatially normalized into the PET template available in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Since T1-weighted MR images of the subjects have been not acquired, the original [^{18}F]FDG images have been directly spatially normalized to the PET template using SPM8 default options. After anatomic standardization, visual inspection revealed a good correspondence in the spatial location of the normalized SUV PET images. Normalized datasets from patients with bipolar disorder and patients with schizophrenia were compared on a voxel-by-voxel basis using a two-sample t statistic test as implemented in SPM8, and adding age as covariate. Indeed, performing a t-test, the ages of the two groups are statistically different ($p=0.001$). 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 only the age had an impact on the results. We also included as a covariate the medication load index computed in accordance to Versace et al. (2008). Group differences were assessed applying a threshold of $p<0.0005$ (uncorrected for multiple comparisons).

3. Results

Metabolic activity corrected at the administration of 18FDG was calculated for both patients with schizophrenia (mean ± S.D. = 122.3 ± 36.8) and with bipolar disorder (mean ± S.D. = 134.5 ± 17.7).

White matter metabolism differed in patients with schizophrenia in comparison to those with bipolar disorder ($p<0.0005$),

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