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Voxelwise evaluation of white matter volumes in first-episode psychosis

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ABSTRACT

The occurrence of white matter (WM) abnormalities in psychotic disorders has been suggested by several studies investigating brain pathology and diffusion tensor measures, but evidence assessing regional WM morphometry is still scarce and conflicting. In the present study, 122 individuals with first-episode psychosis (FEP) (62 fulfilling criteria for schizophrenia/schizophreniform disorder, 26 psychotic bipolar I disorder, and 20 psychotic major depressive disorder) underwent magnetic resonance imaging, as well as 94 epidemiologically recruited controls. Images were processed with the Statistical Parametric Mapping (SPM2) package, and voxel-based morphometry was used to compare groups (*t*-test) and subgroups (ANOVA). Initially, no regional WM abnormalities were observed when both groups (overall FEP group versus controls) and subgroups (i.e., schizophrenia/schizophreniform, psychotic bipolar I disorder, psychotic depression, and controls) were compared. However, when the voxelwise analyses were repeated excluding subjects with comorbid substance abuse or dependence, the resulting statistical maps revealed a focal volumetric reduction in right frontal WM, corresponding to the right middle frontal gyral WM/third subcomponent of the superior longitudinal fasciculus, in subjects with schizophrenia/schizophreniform disorder ($n=40$) relative to controls ($n=89$). Our results suggest that schizophrenia/schizophreniform disorder is associated with right frontal WM volume decrease at an early course of the illness.

1. Introduction

The cerebral white matter (WM) subserves all cognitive and neurological functions through its fiber pathways of axonal connections, constituting distributed neural circuits which link geographically distant regions in cortical and subcortical areas (Schmahmann et al., 2008). Lesions affecting the cerebral WM may result in a number of neuropsychiatric manifestations, and WM abnormalities have been reported to be associated with both psychotic and affective disorders (Walterfang et al., 2006; Zanetti et al., 2009). *Post-mortem* studies found reductions in size and density of oligodendrocytes and abnormal myelin structure and compactness in the WM of schizophrenia patients (Walterfang et al., 2006), whereas glial cell abnormalities have been observed in the brain of bipolar disorder (BD) subjects (McDonald et al., 2004).

Major improvements in neuroimaging techniques have been seen during the past decades, which have allowed increasingly more detailed assessments of structural and functional aspects of the human brain *in vivo* (Busatto et al., 2008). T1-weighted magnetic resonance images allow us to assess total or regional WM volumes (Hulshoff Pol et al., 2004; Plaze et al., 2011), while the more recently developed diffusion tensor imaging (DTI) provides us measures of anisotropy (a measure of fiber density and myelination) and diffusivity (an estimate of the displacement of water molecules in a tissue) (Zanetti et al., 2009).

DTI studies support the existence of WM brain abnormalities in both psychotic and affective disorders (Zanetti et al., 2009; Bora et al., 2011). Two meta-analyses of DTI studies found schizophrenia to be consistently associated with fractional anisotropy reductions in fronto-limbic-striatal WM (Ellison-Wright and Bullmore, 2009; Bora et al., 2011), specially involving the inferior fronto-occipital and longitudinal fasciculi bilaterally, which were observed to be affected even in first-episode patients (Bora et al., 2011). In affective disorders, studies employing DTI techniques have also revealed microstructural WM abnormalities affecting fronto-limbic-striatal circuits (Zanetti et al., 2009; Korgaonkar et al., 2011; Vederine et al., 2011).

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However, the anatomical regions most frequently implicated in bipolar disorder (BD) have been the ventromedial prefrontal WM, and the uncinate and superior longitudinal fasciculi (Zanetti et al., 2009; Vederine et al., 2011), whereas a pattern of limbic-dorsolateral prefrontal-parietal WM abnormalities has been described for major depressive disorder (MDD) (Ma et al., 2007; Wu et al., 2011; Korgaonkar et al., 2011).

A number of magnetic resonance imaging (MRI) morphometry studies have evaluated the occurrence of volumetric WM abnormalities in schizophrenia and BD. Table 1 summarizes the studies which have assessed regional WM volumes or density in first-episode psychosis (FEP) or schizophrenia through voxelwise methods. Although a high heterogeneity of findings is observed across these studies, abnormalities of dorsolateral frontal-striatal WM and of long associative tracts such as the inferior fronto-occipital and longitudinal fasciculi have been often observed (Table 1). Moreover, reductions in total cerebral WM volume were observed in non-affected monozygotic twins of schizophrenia patients (Hulshoff Pol et al., 2004, 2006) and individuals presenting with prodromal psychotic symptoms (Witthaus et al., 2008), suggesting that WM abnormalities are related to an increased genetic liability to schizophrenia. Despite the increasing number of DTI studies in affective disorders, the current amount of evidence for WM morphometry in BD is still limited. Only five studies to date have evaluated regional WM volumes in BD patients (Bruno et al., 2004; McIntosh et al., 2005; Nugent et al., 2006; Scherk et al., 2008; Tost et al., 2010) and their unaffected relatives (McIntosh et al., 2005; van der Schot et al., 2009) – none recruiting first-episode patients – with conflicting results. To our knowledge, there are no studies assessing WM volume abnormalities in psychotic MDD.

In a number of neuroimaging studies of neuropsychiatric disorders over the past decade, automatic voxel-by-voxel comparisons of regional brain indices have been employed as an alternative to conventional region-of-interest (ROI) measurements. When applied for voxelwise comparisons of regional gray and/or white matter volumes between different groups of subjects studied with MRI, this technique is referred to as voxel-based morphometry (VBM) (Ashburner, 2009). Advantages of voxelwise approaches are that these methods allow whole-brain analyses in an automated fashion, without requiring the *a priori* selection of ROIs and with high reproducibility (Busatto et al., 2008). Moreover, even when *a priori* hypotheses can be formulated about disease-related brain abnormalities in specific ROIs, a region of abnormality might be part of an ROI, or span over multiple ROIs, thereby potentially reducing statistical power of the underlying morphological analysis (Fan et al., 2007).

A large sample of FEP patients, with both affective (BD and MDD) and non-affective psychotic disorders, and demographically matched controls were recruited in the same defined geographical area using an epidemiologic approach and underwent structural MRI. We conducted a set of VBM analyses in order to confirm previous literature findings of volumetric WM reductions affecting dorsolateral prefrontal WM and the inferior fronto-occipital and longitudinal fasciculi of first-episode schizophrenia patients, and also to afford a whole-brain exploratory analysis of regional WM volumes in psychotic BD and MDD. Based on previous DTI studies in affective disorders, we hypothesized that BD might be linked to ventromedial prefrontal WM and uncinate fasciculus abnormalities, while a pattern of dorsolateral prefrontal-limbic WM volume reductions might more likely be associated with MDD.

2. Methods

2.1. Participants

The cases for the present study were selected from a sample of 200 FEP subjects who took part in a population-based case–control study investigating the incidence and risk factors for psychotic disorders in a circumscribed region of São Paulo city, formed by 21 districts under the same public health administration and comprising approximately 900,000 inhabitants (Menezes et al., 2007; Schaufelberger et al., 2007). Inclusion criteria for FEP cases in the neuroimaging arm of the study were as follows: (a) current age between 18 and 50 years; (b) residence for 6 months or more in defined geographic areas of Sao Paulo; and (c) diagnosis of a functional psychosis according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition criteria (DSM-IV; American Psychiatric Association, 1994) (295–298, psychotic codes), as assessed by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Cases were identified by active surveillance of all people that made contact for the first time with the mental healthcare services for that region between 2002 and 2005 due to a DSM-IV defined psychotic disorder or psychotic mood episode, regardless of its severity (both outpatients and inpatients were recruited), duration of illness or compliance to treatment (orientation was provided to the patients, but they were referenced to treatment at services in the geographical region where they lived). Patients with psychotic disorders due to a general medical condition or substance-induced psychosis were excluded.

Table 1
Voxel-based morphometry studies of regional white matter (WM) volumes or density in first-episode psychosis or schizophrenia patients.

Study	Sample	MRI scan	Image analysis method[a]	Smoothing[b]	Regions and type of WM abnormality
Chua et al., 2007	26 FEP (DN) 38 HC	1.5 T	BAMM Software Cluster $p<0.05$ (corrected)	4.4 mm	Volume ↓: right anterior limb of anterior capsule, right fronto-occipital fasciculus, bilateral fornices.
Whitford et al., 2007	41 FESZ 47 HC	1.5 T	SPM2 software Peak voxel $p<0.05$ (corrected) Extent threshold = 100 voxels (cluster)	12 mm	Volume ↓: right fronto-occipital fasciculus, corticopontine/thalamocortical fibers, medial frontal gyrus; left inferior longitudinal fasciculus and precentral gyrus. Volume ↑: right postcentral gyrus and left middle frontal gyrus.
Witthaus et al., 2008	23 FESZ 29 HC	1.5T	SPM2 software Uncorrected $p<.001$ Extent threshold = 10 voxels (cluster)	12 mm	Volume ↓: bilateral superior frontal, precentral, and middle temporal gyri; left medial and middle frontal gyri, postcentral and inferior occipital gyri; right thalamic-temporal fibers.
Cocchi et al., 2009	21 FESZ 41 HC	1.5 T	SPM5/ CamBa softwares Cluster-based permutation statistics	12 mm	Density ↓: bilateral corticospinal tract, inferior fronto-occipital and longitudinal fasciculi, anterior thalamic radiation; right forceps major. Density ↑: terminal part of left forceps major, fronto-occipital and longitudinal fasciculi.
Price et al., 2010	48 FEP 47 HC	1.5 T	SPM2 software Peak voxel $p<0.05$ (corrected) Extent threshold = 10 voxels (cluster)	12 mm	Volume ↓: right posterior internal capsule and striatal WM; left striatal WM.
Moriya et al., 2010	19 FESZ 19 HC	3.0 T	SPM5 software Peak voxel $p<0.05$ (corrected)	12 mm	No between-group differences were observed in regional WM volumes.

Abbreviations: FEP, first-episode psychosis; FESZ, first-episode schizophrenia; HC, healthy controls; DN, drug naïve; WM, white matter. ↑ = increase; ↓ = reduction.
[a] Image processing method and statistical threshold.
[b] Full-width half-maximum (FWHM) Gaussian kernel.