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Brain white matter microstructure in deficit and non-deficit subtypes of schizophrenia

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ABSTRACT

Dividing schizophrenia into its deficit (SZD) and nondeficit (SZND) subtypes may help to identify specific and more homogeneous pathophysiological characteristics. Our aim was to define a whole brain voxelwise map specifically characterizing white matter tracts of schizophrenia patients with and without the deficit syndrome. We compared microstructural diffusion-related parameters as measured by diffusion tensor imaging in 21 SZD patients, 21 SZND patients, and 21 healthy controls, age- and gender-matched. Results showed that fractional anisotropy was reduced in the right precentral area in SZND patients, and in the left corona radiata of the schizophrenia group as a whole. Axial diffusivity was reduced in the left postcentral area of SZD patients and in the left cerebellum of the whole schizophrenia group. Radial diffusivity was increased in the left forceps minor of SZD patients, in the left internal capsule of SZND patients, and in the right inferior fronto-occipital fasciculus in the whole schizophrenia group. Mean diffusivity was increased from healthy controls to SZD patients to SZND patients in the right occipital lobe. In conclusion, SZD patients are not simply at the extreme end of a severity continuum of white matter disruption. Rather, the SZD and SZND subtypes are associated with distinct and specific brain microstructural anomalies that are consistent with their peculiar psychopathological dimensions.

1. Introduction

One approach to the study of schizophrenia is based on the separation of a homogeneous subgroup of patients characterized by negative symptoms that are primary, stable and enduring; the subgroup has been called *deficit schizophrenia* (SZD) group (Carpenter et al., 1988; Kirkpatrick et al., 2001; Galderisi and Maj, 2009). Subjects with SZD seem to be at the extreme end of a continuum of patients presenting negative symptoms. However, Carpenter and his associates introduced (Carpenter et al., 1988) and then validated (Buchanan et al., 1990; Kirkpatrick et al., 1993, 1994, 2001; Amador et al., 1999) the idea that SZD is a separate disorder and not simply a more severe form of schizophrenia compared with patients characterized as belonging to the non-deficit subgroup (SZND). Several studies have explored socio-demographic characteristics (Galderisi et al., 2002; Messias et al., 2004), risk factors (Kirkpatrick et al., 2000a), clinical outcome (Carpenter, 1994; Tek et al., 2001), response to treatment (Kirkpatrick et al., 2000b) and neurobiological features (Kirkpatrick and Buchanan, 1990; Ross et al., 1997; Waltrip et al., 1997; Hong et al., 2005) associated with SZD. Some studies have demonstrated double dissociations (SZD patients impaired on measure A but not B; SZND patients impaired on measure B but not A) in metabolic measures (Garcia-Rizo et al., 2012), season of birth (Messias et al., 2004), and electrophysiological variables (Mucci et al., 2007). These studies are consistent with the concept that SDZ is a separate disorder within the syndrome of schizophrenia.

Early positron emission tomography investigations described SZD patients as characterized by thalamic, frontal and parietal hypometabolism (Tamminga et al., 1992; Heckers et al., 1999). More recently, single photon emission tomography studies showed reduced cerebral blood flow in SZD with respect to SZND in frontal (Gonul et al., 2003; Kanahara et al., 2013) and bilateral frontodorsolateral (Vaiva et al., 2002) cortices. Moreover, using magnetic

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resonance spectroscopy, Delamillieure and colleagues interpreted a reduced concentration of *N*-acetyl aspartate in the medial prefrontal cortex of SZD as an indicator of neuronal impairment in that region (Delamillieure et al., 2000). Structural magnetic resonance imaging (MRI) studies found either structural anatomical anomalies in SZD in comparison with SZND or the contrary. In particular, Buchanan and colleagues (Buchanan et al., 1993) and Galderisi and co-workers (Galderisi et al., 2008), respectively, described increased prefrontal volumes and reduced lateral ventricles in SZD compared with SZND patients. In contrast, the groups of Arango (Arango et al., 2008) and Fischer (Fischer et al., 2012) found SZD patients to be more impaired than SZND patients and healthy controls (HC), observing respectively larger ventricles and smaller temporal gray matter volume in SZD. Damage to white matter (WM) microstructure was also reported to characterize the brains of SZD patients (Rowland et al., 2009; Kitis et al., 2012; Voineskos et al., 2013). The studies examining WM focused on tracts that were a priori selected (Rowland et al., 2009; Voineskos et al., 2013) or on regions of interest (ROIs) (Kitis et al., 2012); they all pinpointed WM disruptions in selected areas as a neurobiological feature of SZD. If on the one hand choosing an a priori region may decrease the possibility of false positive results, on the other hand it may increase the probability of false negative results. Moreover, ROI-based studies in SZD found heterogeneous results and, to date, the picture of neuroanatomical regions that are pivotal in SZD is far from being clear. In this framework, a whole brain voxel-based investigation probing WM changes in SZD and SZND patients with respect to HC subjects is needed. Such an approach is important to detect brain differences in brain WM as a whole, particularly in the attempt to define whether between-group brain alterations are distributed over multiple foci rather than in specific and predetermined brain regions (Voormolen et al., 2010; Perlini et al., 2012).

The aim of the present study was to reveal a WM voxel-by-voxel microstructural map defining neuroanatomical areas peculiarly impaired in SZD, SZND or in schizophrenia as a whole. A HC group was selected to test the hypothesis of a severity continuum in the framework of WM microstructure.

Given the known WM abnormalities identified in schizophrenia patients in our previous works (Spalletta et al., 2003; Spoletini et al., 2009; Chiapponi et al., 2013), we hypothesized (1) that we would find WM abnormalities in the whole group of patients with respect to HC subjects; (2) that we would find significant differences between SZD and SZND in terms of microstructural diffusion-related indices. However, due to the complexity and variety of results found in previous studies on SZD, we made a general prediction that we would find localized brain regions in which the deficit subgroup would show specific impairment, and other brain regions in which the non-deficit subgroup would be the most impaired.

2. Methods

2.1. Subjects

For this study we initially included 42 SZD patients consecutively recruited at the IRCCS Santa Lucia Foundation of Rome. The diagnosis of schizophrenia was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) (American Psychiatric Association, 2000). The clinician treating the patients, who was blind to the aims of the study, made the preliminary diagnosis. Then, a senior research psychiatrist confirmed all preliminary diagnoses using the Structured Clinical Interview for DSM-IV-TR-Patient Edition (SCID-I/P) (First et al., 2002a). A semi-structured interview, the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), was used to diagnose SZD with standard criteria. The SZD subtype was diagnosed conservatively with the aim of minimizing false positive diagnoses. Using a retrospective method, the same senior psychiatrist who confirmed all the DSM diagnoses reviewed information regarding the patients clinical status during the preceding 12 months. The senior psychiatrist was trained by B.K. at the Maryland Psychiatric Research Center. The information required to compile the SDS was obtained from review of records and interviews with psychiatrists and other mental health professionals who treated the patients and had long-standing contact with them. In addition, reports from the patients and first degree relatives were used to integrate the data reported by the clinical staff. According to SDS criteria, the final diagnosis of SZD required some combination of two or more primary negative symptoms always to be present for the 12 months preceding the admission.

From the original group of patients confidently diagnosed as SZD, four refused to undergo MRI, 11 were excluded for strong movement artefacts in brain images, and six were excluded for the presence of moderate to severe brain vascular lesions (see exclusion criteria below). The remaining 21 SZD patients were age- and gender-matched with 21 SZND patients. This latter group was selected from an original sample of 96 SZND patients consecutively recruited at the IRCCS Santa Lucia Foundation in Rome.

Overall severity of psychiatric symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Age at onset was defined as age at onset of positive or negative symptoms preceding the first hospitalization, which was investigated in an interview with patients and first degree relatives.

All patients were receiving stable oral dosages of one or more atypical antipsychotics such as risperidone, quetiapine, and olanzapine. Antipsychotic dosages were converted to equivalents of olanzapine (Oquendo et al., 2003). Extrapyramidal side effects and abnormal involuntary movements were evaluated using the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976).

We also recruited 21 HC subjects carefully matched, one by one, with SZD and SZND patients for age and gender. All HC subjects were screened for a current or lifetime history of DSM-IV-TR Axis I and II disorders using the SCID-I/NP (First et al., 2002b) and SCID-II (First et al., 1997); they were also assessed to confirm that no first degree relative had a history of psychosis.

Inclusion criteria for all participants were as follows: (1) age between 18 and 65 years, (2) at least 8 years of education, and (3) suitability for MRI scanning. Exclusion criteria were as follows: (1) history of alcohol or drug abuse in the 2 years before the assessment, (2) lifetime drug dependence, (3) traumatic head injury with loss of consciousness, (4) past or present major medical illness or neurological disorders, (5) any additional psychiatric disorder or mental retardation, (6) dementia or cognitive deterioration according to DSM-IV-TR criteria and Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score lower than 25, consistent with normative data in the Italian population (Measso et al., 1993), and (7) any potential brain abnormality and microvascular lesion as apparent on conventional fluid attenuated inversion recovery (FLAIR) scans; in particular, the presence, severity, and location of vascular lesions were computed according to the semi-automated method recently published by our group (Iorio et al., 2013).

Sociodemographic and clinical characteristics of the HC, SZD and SZND samples are shown in Table 1.

The study was approved and undertaken in accordance with the guidelines of the Santa Lucia Foundation Ethics Committee. All participants gave their written informed consent to participate after they had received a complete explanation of the study procedures.

2.2. Image acquisition and processing

All 63 participants underwent the same imaging protocol, which included 3D T1-weighted, diffusion tensor imaging (DTI), T2-weighted and FLAIR sequences using a 3T Allegra MR imager (Siemens, Erlangen, Germany) with a standard quadrature head coil. Whole-brain T1-weighted images were obtained in the sagittal plane using a modified driven equilibrium Fourier transform sequence (TE/TR=2.4/7.92 ms, flip angle 15°, voxel size $1 \times 1 \times 1$ mm^3).

Diffusion-weighted volumes were acquired using spin-echo EPI (TE/TR=89/8500 ms, bandwidth=2126 Hz/vx; matrix size 128×128; 80 axial slices, voxel size $1.8 \times 1.8 \times 1.8$ mm^3, scan time 12 min) with 30 isotropically distributed orientations for the diffusion-sensitising gradients at a *b*-value of 1000 s/mm^2 and no diffusion weighted images (b0). Scanning was repeated three times to increase the signal-to-noise ratio (Cherubini et al., 2009).

Diffusion-weighted images were processed using FSL 4.1 software (www.fmrib.ox.ac.uk/fsl/). Diffusion-weighted images were corrected for the distortion induced by eddy currents and head motions, by applying a 3D full affine alignment of each image to the mean b0 image. After distortion corrections, DTI data were averaged and concatenated into 31 (1 b0+30 b1000) volumes. A diffusion tensor model was fitted at each voxel, generating fractional anisotropy (FA), axial diffusivity (AD) (first eigenvalue of the diffusion tensor), radial diffusivity (RD) (average of the second and third eigenvalues) and mean diffusivity (MD) maps.

We used TBSS (Smith et al., 2006) version 1.2, part of FSL for the post-processing and analysis of FA, RD, AD and MD maps in WM. The key features of TBSS overcome the alignment problems (Simon et al., 2005; Vangberg et al., 2006) and smoothing issues (Jones et al., 2005) related to conventional voxel-based morphometry (VBM) whole brain approaches for multi-subject DTI. Briefly, TBSS first projects all subjects' FA, RD, AD and MD data onto an alignment invariant tract representation, the skeleton, by means of the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). This process of projecting individual maps onto a mean skeleton helps to