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Research report

Cognitive performances associate with measures of white matter integrity in bipolar disorder

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ABSTRACT

Background: Neuropsychological deficits constitute enduring trait-like features in bipolar disorder (BD), and persist in euthymia. White matter (WM) abnormalities are one of the most consistently reported findings in neuroimaging studies of BD. We hypothesized that neuropsychological performances could correlate with WM integrity in a sample of bipolar patients in core WM tracts.
Methods: Seventy-eight patients affected by BD were evaluated for verbal memory, working memory, psychomotor coordination, executive functions, attention and information processing, and verbal fluency through the Brief Assessment of Cognition in Schizophrenia. White matter integrity was evaluated using DTI and tract-based spatial statistics with threshold free cluster enhancement ($p > 0.949$).
Results: We observed that cognitive performances in attention and information processing, working memory, executive functions and psychomotor coordination were associated with DTI measures of WM integrity in several association fibres: inferior and superior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, corpus callosum, and corona radiata.
Limitation: The drug treatments administered during the course of the illness could have influenced DTI measures and neurocognitive function. Other limitations include issues such as generalizability due to the lack of a control group, possible undetected past comorbidities, population stratification, and the presence of a 28% of patients which previously experienced delusions.
Conclusions: This is the first study to use a validated cognitive battery to investigate the principal cognitive domains in BD. Our data confirm the importance of WM integrity as a neurobiological underpinning of cognitive deficits.

1. Introduction

Bipolar disorder is a common disabling illness characterized by a recurrent and episodic course involving disturbances of mood, sleep, behaviour, perception, and cognition (Goodwin and Jamison, 2007), with a lifetime morbid risk of approximately 4% (Ketter, 2010). It is estimated that 30–50% of largely remitted bipolar patients fail to attain premorbid levels of psychosocial functioning and much of this disability may be linked to cognitive impairment (Goodwin and Jamison, 1990). Cognitive dysfunction in bipolar disorder is usually not as dramatic as in schizophrenia and can be confused with anxiety or other comorbid features of mood disorder. Cognitive deficits persist despite clinical improvement (Poletti et al., 2014) and although the euthymic state has been associated with better performances compared to the other states, it still involves cognitive impairment in comparison with healthy controls (Malhi et al., 2007, 2004). Neuropsychological deficits are thus considered enduring trait-like features of BD (Burdick et al., 2006; Hill et al., 2009).

In 1965, Norman Geschwind, asserted that disconnection syndromes resulting from white matter lesions could underlie deficits in higher-order functions, thereby advancing the idea that disconnection of grey matter regions, by interrupting the communication between them, could be as disruptive as trauma to those regions per se.

White matter (WM) abnormalities are one of the most consistently reported findings in neuroimaging studies of BD. Given the microscopic structure of WM, in normal conditions the integrity of myelinated axons limits the diffusion of water in directions other than along the main axis of the fibre. This tendency to diffuse in one direction as opposed to all others, termed anisotropy, reflects the integrity of axons and myelin sheaths and the bundle coherence of WM tracts, and can be estimated in vivo through the application of diffusion-tensor imaging (DTI) techniques (Basser et al., 1994; Le Bihan, 2003; Taylor et al., 2004). These allow to estimate the tendency to diffuse along the principal direction of the fibre (axial diffusivity, AD) or perpendicular to axonal walls (radial diffusivity,

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RD) (Song et al., 2002), and to calculate the variance of the direct measures of the diffusion magnitude in these directions (fractional anisotropy, FA).

Few studies have investigated the association between WM integrity and cognitive impairment. White matter hyperintesities have been reported in the frontal lobes and basal ganglia, which are critical for executive function, attention, speeded information processing, learning and memory, and affect regulation (Bearden et al., 2001). The presence and severity of white matter hyperintesities inversely correlated with decreased performance on a range of cognitive tasks in BD (Dupont et al., 1990; Krabbendam et al., 2000), and FA positively correlated with verbal memory and working memory performances (James et al., 2011). Reduced FA in the anterior limb of the internal capsule correlated significantly with an increased number of errors during set shifting and increased risk taking, and reduced FA in uncinate fasciculus correlated significantly with increased risk taking (Linke et al., 2013). Increased MD in the fornix, anterior thalamic radiation, splenium and the body of the corpus callosum associated with poorer performance in executive tasks in BD patients (Oertel-Knochel et al., 2014).

Considering the widespread WM disruption observed in BD, we hypothesized that cognitive impairment will be associated to WM abnormalities. The aim of the present study was to investigate the DTI correlates of neuropsychological performances in a sample of bipolar patients.

2. Methods

2.1. Sample

The sample included 78 biologically unrelated in patients with a diagnosis of Bipolar Disorder I (DSM-IV criteria, SCID-I interview) in course of a depressive episode. Exclusion criteria were: additional diagnoses on axis I, mental retardation on axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency. 27% of patients was taking lithium medication from at least 6 months. 28% of patients had a history of previous delusional episodes but did not experiences delusions at the time of the evaluation. Physical examination, laboratory tests and electrocardiograms were performed at admission. No patient received electroconvulsive therapy (ECT) within 6 months prior to study enrolment. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the local ethical committee.

2.2. Clinical and Neuropsychological Assessment

Severity of depression was rated on a modified version of the 21-item Hamilton Depression Rating Scale (HDRS). Severity of mania was rated on the Young Mania Rating Scale (YMRS).

Cognitive functions have been assessed through the Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004), a broad battery evaluating several domains of cognition (verbal memory, working memory, psychomotor speed and coordination, selective attention, semantic fluency, letter fluency and executive functions). Normative Italian adjusted scores (Anselmetti et al., 2008) were used for the BACS subtests. In order to investigate executive functions, the BACS battery employs the Tower of London Test. However, while there is a substantial agreement across studies upon an impaired performance at the Wisconsin Card Sorting Test (WCST), mixed findings have been reported on the same patients on many measures of the Tower of London task, with some investigators reporting impairments and others not (Glahn and Bearden, 2007). In the present study we then replaced the Tower of London task with the WCST. WCST normative Italian adjusted scores (Laiacona et al., 2000) were used to evaluate the goodness of executive functions performances. All tests were administered by a trained psychologist. To provide a standard metric for comparison across neurocognitive domains for each subtest an equivalent score, ranging from 0 to 4, has been obtained where score of 2, 3 or 4 reveal a good performance while score of 0 or 1 reveal a poor performance. Standardized domain scores were calculated for symbol coding (selective attention), digit sequencing (working memory), verbal memory, token motor task (psychomotor coordination), verbal fluency and WCST (executive functions). For WCST a global score was calculated to represent an overall index of performance. It estimates how many cards the subject actually uses in excess of the minimum necessary to achieve the six categories (or the possibly lowest number of categories effectively detected). The global score is computed by subtracting from the total number of administered trials the number of categories completed multiplied by 10 (as 10 is the number of correct matches required for each category). The global score ranges from a worst of 128 to a theoretical best of 0, i.e. the lower the score, the better the performance.

2.2.1. Image acquisition

Diffusion tensor imaging was performed on a 3.0 Tesla scanner (Gyroscan Intera, Philips, Netherlands) using SE Eco-planar imaging (EPI) and the following parameters: TR/TE=8753.89/58 ms, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix $2.14 \times 2.71 \times 2.31$; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88×1.87 mm^2; SENSE acceleration factor=2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value=900 s/mm^2. Fat saturation was performed to avoid chemical shift artefacts. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), T2 axial slices (TR=3000 ms; TE=85 ms; flip angle=90°; turbo factor 15; 5-mm-thick, axial slices with a 512×512 matrix and a 230×230 mm^2 field of view) were acquired to rule out brain lesions.

2.2.2. Data processing and analyses

Image analyses and tensor calculations were done using the "Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library" (FSL 5.0; www.fmrib.ox.ac.uk/fsl/index.html) (Smith et al., 2004; Woolrich et al., 2009). First, each of the 35 DTI volumes was affine registered to the T2-weighted $b=0$ volume using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001). This corrected for motion between scans and residual eddy-current distortions present in the diffusion-weighted images. In addition, trained researchers blind to diagnosis manually inspected each volume of each image to check for head motion artefacts and exclude those having severe artefacts. Anisotropy can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, i.e. the three eigenvalues λ_1, λ_2 and λ_3(Basser et al., 1994; Le Bihan, 2003; Taylor et al., 2004). The tendency to diffuse along the principal direction of the fibre (AD, λ_1), is the principal diffusion eigenvalue (λ_1) and reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius et al., 2012). An increase in radial diffusivity (RD, the average of λ_2 and λ_3), perpendicular to axonal walls, suggests disrupted myelination (Song et al., 2002). Mean diffusivity (MD, average of λ_1, λ_2 and λ_3) is a measure of the average molecular motion, independent of tissue directionality. Fractional anisotropy (FA) is the square root of the sum of squares (SRSS) of the diffusivity differences, divided by the SRSS of the three diffusivities. After removal of nonbrain tissue (Smith, 2002), least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps.

Next, all individuals' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (Smith