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Research paper

Patterns of microstructural white matter abnormalities and their impact on cognitive dysfunction in the various phases of type I bipolar disorder

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ABSTRACT

Background: In recent years, diffusion tensor imaging (DTI) studies have detected subtle microstructural abnormalities of white matter (WM) in type I bipolar disorder (BD). However, WM alterations in the different phases of BD remain to be explored. The aims of this study is to investigate the WM alterations in the various phases of illness and their correlations with clinical and neurocognitive features.
Methods: We investigated the DTI-derived fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) in patients with type I BD ($n=61$) subdivided in manic ($n=21$), depressive ($n=20$) and euthymic phases ($n=20$) vs. healthy controls ($n=42$), using a tract-based spatial statistics (TBSS) approach. Then, we investigated whether the subgroups of patients in the various phases of illness present different patterns of WM abnormalities. Finally we studied the correlations between WM alterations and clinical-cognitive parameters.
Results: We found a widespread alteration in WM microstructure (decrease in FA and increase in MD and RD) in BD when compared to controls. The various subgroups of BD showed different spatial patterns of WM alterations. A gradient of increasing WM abnormalities from the euthymic (low degree and localized WM alterations mainly in the midline structures) to the manic (more diffuse WM alterations affecting both midline and lateral structures) and, finally, to the depressive phase (high degree and widespread WM alterations), was found. Furthermore, the WM diffuse alterations correlated with cognitive deficits in BD, such as decreased fluency prompted by letter and decreased hits and increased omission errors at the continuous performance test.
Limitations: Patients under treatment.
Conclusions: The WM alterations in type I BD showed different spatial patterns in the various phases of illness, mainly affecting the active phases, and correlated with some cognitive deficits. This suggests a complex trait- and state-dependent pathogenesis of WM abnormalities in BD.

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1. Introduction

Bipolar disorder (BD) type I is a chronic mental disease (1–2% in general population) associated with high rates of non-recovery, psychiatric and medical comorbidity, and progressive cognitive deterioration (especially in attention and executive functioning) (A.P.A., 1994; Akiskal, 1996; Quraishi and Frangou, 2002). Since a growing number of neurobiological abnormalities have been recently reported in patients affected by BD (Frangou, 2014; Savitz et al., 2013; Soares and Mann, 1997), magnetic resonance imaging (MRI) has become a relevant non-invasive tool to investigate *in-vivo* the pathophysiology of the disease (Heng et al., 2010).

Diffusion tensor imaging (DTI) is a MRI technique particularly suited for the study of white matter (WM) microstructure and provides relevant information about fiber integrity and orientation (Heng et al., 2010). Previous DTI studies have reported subtle microstructural abnormalities of WM in BD, characterized by a loss of WM network connectivity involving not only prefrontal regions but also projection, associative and commissural fiber tracts (Heng et al., 2010; Nortje et al., 2013; Vederine et al., 2011; Wise et al., 2015). Owing to the widespread nature of WM abnormalities, a few of these DTI studies of patients with BD employed a tract-based spatial statistics (TBSS) approach that allows a whole brain analysis in an automated and reliable fashion, thus providing a global perspective of WM alterations (Heng et al., 2010). The previous TBSS studies in BD confirmed that all major classes of tracts are implicated, but included only adult patients in euthymic/remitted or depressed phase (Bauer et al., 2015; Benedetti et al., 2011a; 2011b; Chan et al., 2010; Emsell et al., 2013; Heng et al., 2010; Kumar et al., 2015; Lagopoulos et al., 2013; Mahon et al., 2012; Nortje et al., 2013; Oertel-Knochel et al., 2014; Poletti et al., 2015; Sprooten et al., 2013; Vederine et al., 2011; Versace et al., 2008; 2010; Wessa et al., 2009; Wise et al., 2015; Yip et al., 2013).

Since none of these studies included and directly compared the various phases of type I BD, it is still not clear whether WM abnormalities are prevalent in the active states or whether they are present in all the phases of BD (i.e. trait- and/or state-dependent). Since type I BD presents a cyclic pattern with dramatic changes in clinical states across the different phases, showing acute phases characterized by full blown and opposite psychopathological states (mania and depression), as well as subclinical states similar to healthy (euthymia), the investigation of state-dependent brain changes assumes particular relevance in this illness. Some functional and metabolic data suggest state dependent changes across the different phases of BD (Brady et al., 2012; Fountoulakis et al., 2008; Magioncalda et al., 2015; Pomarol-Clotet et al., 2015). Beyond functional changes, recent evidences in DTI studies suggest that dynamic changes also occur in the WM microstructure, both in healthy after learning-induced plasticity (Imfeld et al., 2009; Oechslin et al., 2009; Scholz et al., 2009) and in depressed patients when compared to those in remission (Bracht et al., 2015; Zanetti et al., 2009). However, to date, WM alterations in all the various phases of type I BD – i.e., including at the same time mania, depression and euthymia – have yet to be investigated.

Moreover, WM abnormalities may play a role at a clinical level. BD is associated with various cognitive deficits, whose profile changes across the different phases of illness (Quraishi and Frangou, 2002). The different impairment of some cognitive domains among the different phases of BD, especially between active phases and euthymia, could depend on several factors, including potential dynamic changes of WM microstructure across the phases of illness. Although a few DTI studies in depressed and euthymic patients showed that WM abnormalities are associated with cognitive deficits (Bauer et al., 2015; Oertel-Knochel et al., 2014; Poletti et al., 2015), the impact of WM abnormalities on cognitive dysfunctions in patients in all the various phases of type I BD remains still unclear.

Therefore, the aims of our study were to: (i) investigate the presence and extent of WM abnormalities as measured by DTI-derived fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) in patients with type I BD in any phase of illness (i.e. depressive, manic and euthymic phases); (ii) determine whether the subgroups of patients in the various phases of illness present different patterns of WM abnormalities; and (iii) explore the relationship of WM alterations with cognitive and clinical parameters.

2. Methods

2.1. Subjects and clinical assessment

Subjects were admitted to the in-patients and out-patients service of the Psychiatric Clinic at the University of Genoa (IRCCS AOU San Martino – IST, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health), from 2013 to 2015. The study was conducted on 61 type I bipolar patients (43 females, 18–60 years old, 21 in manic phase, 20 in depressive phase and 20 in euthymic phase) and 42 healthy participants (Table 1). The Ethical Committee of San Martino Hospital approved the study, and written informed consent was obtained from all the participants.

Each participant was evaluated using the following standardized structured and/or semi-structured clinical instruments to obtain information on clinical and diagnostic features, course of illness, family history, and actual and past pharmacotherapy: Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); Structured Clinical Interview for Axis-I Disorders/Patient edition (SCID-I/P) (Ventura et al., 1998); Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1994); Structured Interview for Mood Disorder – Revised (SIMD-R) (Cassano et al., 1989); Hamilton Depression Scale (HAM-D) with 17 items (Hamilton, 1960); Young Mania Rating Scale (YMRS) (Young et al., 1978). General, physiologic, pathologic and psychopathologic history was also investigated.

Inclusion criteria were: (a) diagnosis of type I BD according to the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV) criteria (A.P.A., 1994) assessed by the SCID-I/P (Ventura et al., 1998) (for manic, depressed and euthymic patients); (b) score ≥ 18 at HAM-D with 17 items (Hamilton, 1960) and/or score ≥ 13 at YMRS (Young et al., 1978) (for manic and depressed patients); HAM-D score < 8 (Hamilton, 1960) and YMRS score < 8 (Young et al., 1978) for euthymic patients; (c) age between 18 and 60; (d) ability to provide written informed consent. Exclusion criteria were: (a) diagnoses of schizophrenia, mental retardation, dementia and other cognitive disorders; (b) history of severe or decompensated somatic diseases, neurological diseases (e.g. former stroke, cerebral vascular malformations, or epilepsy), previous head injury with loss of consciousness (for 5 or more minutes); (c) current alcohol and substance abuse (during the previous 3 months); history of alcohol or substance dependence; history of synthetic and new drugs abuse; (d) pregnancy and lactation; (e) left-handed; (f) the inability to undergo an MR examination (claustrophobia, metal implants, etc); (g) previous treatment with electroconvulsive therapy, chemotherapy or brain radiotherapy. Healthy participants did not meet the DSM-IV criteria for psychiatric disorders, either currently or in the past; they had a score at HAM-D < 8 and at YMRS < 8; they also met the same exclusion criteria indicated for patients.

A brief cognitive assessment was carried out on all participants. We chose to focus on the assessment of attention and executive functions not only because they are the most affected cognitive