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Exploring mania-associated white matter injury by comparison with multiple sclerosis: a diffusion tensor imaging study

Niccolò Piaggio[a,b], Simona Schiavi[a], Matteo Martino[b,c,*], Giulia Bommarito[a,b], Matilde Inglese[a,b,d], Paola Magioncalda[b,c]

[a] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Neurology, University of Genoa, Genoa, Italy
[b] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genova, Genoa, Italy
[d] Department of Neurology, Radiology and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, United States

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ABSTRACT

Bipolar disorder (BD), especially in its active phases, has shown some neuroimaging and immunological similarities with multiple sclerosis (MS). The objective of this study was to compare white matter (WM) alterations in BD patients in manic phase (M-BD) and MS patients at early stage of disease and with low lesion burden. We compared diffusion tensor imaging (DTI)-derived fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) in *a priori* selected WM regions (i.e., corpus callosum and cingulum) betwixt 23 M-BD, 23 MS patients and 46 healthy controls. Both M-BD and MS showed WM changes in the corpus callosum, which, however, showed a greater impairment in MS patients. However, considering the different sub-regions of corpus callosum separately (i.e., genu, body, splenium), M-BD and MS presented an opposite pattern in spatial distribution of WM microstructure alterations, with a greater impairment in the anterior region in M-BD and in the posterior region in MS. Common features as well as divergent patterns in DTI changes are detected in M-BD and early MS, prompting a deeper investigation of analogies and differences in WM and immunological alterations of these disorders.

1. Introduction

Bipolar Disorder (BD) is a recurrent, chronic and debilitating mental disorder, characterized by the occurrence of active phases of illness - i.e., mania and depression - alternated to asymptomatic periods - i.e., euthymia (A.P.A., 2013). In recent years, diffusion tensor imaging (DTI) studies consistently detected widespread white matter (WM) microstructural alterations, especially located in the anterior part of corpus callosum and cingulum (Vederine et al., 2011; Wise et al., 2015). In particular, WM alterations were found to be predominant in the active phases of BD rather than in euthymia, and associated with decreased structural connectivity in midline brain regions in manic patients only, suggesting complex dynamic changes in WM microstructure to occur across the various phases of this illness (Magioncalda et al., 2015; Martino et al., 2016). The DTI changes detected in BD were suggested to reflect alterations in oligodendroglial and WM myelin microstructure (Heng et al., 2010; Versace et al., 2014), which, in turn, have been related to T cell-mediated pathogenesis in various diseases (Willing and Friese, 2012). Interestingly, several studies have shown that BD is associated with distinct immunological abnormalities in the peripheral circulation and central nervous system, regarding both cytokines and immune cells (Anderson and Maes, 2015; Kupka et al., 2000; Reus et al., 2015). Therefore, such DTI abnormalities could hypothetically underlie an inflammatory substrate which dynamically changes through the different phases of disease (Magioncalda et al., 2015; Magioncalda et al., 2018; Martino et al., 2016). In this context, in our recent work, both prominent WM alterations (mainly in the corpus callosum) and immunological changes (mainly in effector CD8+ T cells subpopulations) were found to be strongly associated to mania specifically (Magioncalda et al., 2018). Together, these findings suggest the occurrence of an acute immune response with related WM damage in manic patients, a phenomenon reminiscent of what is observed in chronic inflammatory neurological diseases such as multiple sclerosis (MS) (Magioncalda et al., 2018).

MS is the prototype of inflammatory demyelinating diseases of the central nervous system, characterized by multifocal WM demyelination, gliosis and neuroaxonal damage leading to irreversible clinical disability (Vidal-Jordana and Montalban, 2017). Although widespread

* Corresponding author at: Clinica Psichiatrica, Ospedale Policlinico San Martino, Largo R. Benzi 10, Genoa 16132, Italy.
E-mail address: matteomartino9@gmail.com (M. Martino).

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demyelinating WM lesions (WML) are the hallmark of the disease and are visible on standard T2-weighted magnetic resonance imaging (MRI) scans as hyperintensities (Miller et al., 2014), the disease spreads beyond the MRI visible lesions (Filippi and Rocca, 2005) to the normal-appearing WM (NAWM) (Inglese and Bester, 2010). Advanced MRI techniques, such as DTI, allow to detect and quantify subtle microstructural alterations in NAWM, thus providing a more accurate assessment of WM impairment in the early stages of MS, when the MRI visible lesions are still few (Fox, 2008). The corpus callosum and, in general, the periventricular WM regions are vulnerable sites for lesion development, especially in the early stages of MS (Kincses et al., 2011; Roosendaal et al., 2009). Previous DTI studies in MS have shown decreased fractional anisotropy (FA) and increased mean diffusivity (MD) and radial diffusivity (RD) values (Alexander et al., 2007; Inglese and Bester, 2010; Roosendaal et al., 2009) especially within the T2-visible WML, where such alterations were correlated to pathological findings such as demyelination, axonal loss, inflammation and gliosis (Schmierer et al., 2007). Although to a lesser degree, DTI parameters were reported consistently altered in NAWM of MS patients (reduced FA, augmented MD and RD) [22]; this was related to clinical severity and disease duration (Pulizzi et al., 2007; Rovaris et al., 2002), as well as with neuropathological signs (patchy edema, glial hyperplasia, demyelination, transection-induced axon degeneration, perivascular infiltration containing T lymphocytes) (Allen and McKeown, 1979; Peterson et al., 2001; Salou et al., 2015).

1.1. Aims of the study

According to these data, although BD is not a primarily demyelinating disorder, it seems to share with MS some neurobiological inflammatory features (in particular its manic phase). To our knowledge, a direct DTI metrics comparison between these two diseases has not been performed yet. Therefore, we sought to characterize DTI similarities or differences in the regional extent of WM pathological changes, between patients with mania and MS patients with early disease and small number of WML. We focused our analysis on the corpus callosum and cingulum, considering the consistent alteration found in these structures across both the diseases.

2. Methods

2.1. Subjects

Psychiatric patients affected by type I BD in manic phase were prospectively enrolled in this study. MS patients enrolled in a study to investigate predictors of conversion to MS were selected for the MRI comparative study. Only MRI data from early MS patients matched for sex and age to the BD patients were used.

The bipolar mania (M-BD) group was composed by 23 patients, recruited from the Psychiatric Clinic of the University of Genoa, and part of samples used in previous work (Magioncalda et al., 2015; Magioncalda et al., 2018; Martino et al., 2016). Type I BD diagnosis was assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders (DSM) Axis-I Disorders/Patient edition (SCID-I/P) (Ventura et al., 1998) in accordance to DSM criteria (A.P.A., 2013), and manic patients were included in the study when scoring ≥ 13 at Young Mania Rating Scale (YMRS) (Young et al., 1978) and <8 at 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960).

MRI data from 23 patients with a recent diagnosis of relapsing-remitting MS (RR-MS) according to McDonald's (2010) criteria (Polman et al., 2011) and participating in an ongoing longitudinal study (Bommarito et al., 2017) were selected, in order to obtain a group of patients with a minimum WM lesion burden and sex and age-matched to the M-BD group. Clinical diagnosis was also supported by neurophysiological and cerebrospinal fluid findings. The MRI scan was performed at least one month after steroid administration or the last relapse. Median Expanded Disability Status Scale (EDSS) score was 1.5 (range 0–2.5).

Table 1
Subject demographic information.

Group	M-BD (23)	HC (M-BD) (23)	MS (23)	HC (MS) (23)
Sex (F / M)	14 / 9	14 / 9	14 / 9	14 / 9
Age (Mean ± STD)	42 ± 12	44 ± 12	40 ± 11	30 ± 4.5

Abbreviations: M-BD = mania - bipolar disorder; HC = healthy controls; MS = multiple sclerosis; F = female; M = male; STD = standard deviation.

For each patients' sample (i.e., M-BD and MS) a corresponding 23-subject-population of matched healthy controls (HC) - HC(M-BD) and HC(MS) groups respectively - was included (Table 1).

Exclusion criteria for all groups were: inability to provide written informed consent, diagnosis of other psychiatric, neurologic or cognitive affections, any major systemic or organ comorbidities, history of present or previous drug and/or alcohol addiction, left-handedness, pregnancy and lactation, the inability to undergo an MRI examination.

Both studies on BD and MS were approved by the local Ethical Committee of San Martino Polyclinic Hospital, and all subjects provided written informed consent.

2.2. Magnetic resonance imaging acquisition

All scans were acquired on the same MRI 1.5T General Electric Signa HDX 15.0 scanner, using a standard brain T/R 8-channel phased-array coil. The DTI protocol was always oriented on the pure (scanner's) axial plane and shared these same identical parameters within all subjects: single shot echo planar imaging sequence, five b = 0 acquisitions before the subsequent b = 1000 s/mm^2 diffusion weighted acquisitions, TR = 14000 ms, minimum TE, in-plane matrix 128 × 128, FOV = 240 mm, NEX = 1, 56 contiguous slices, slice thickness = 2.5 mm, no gap. The total number of non-collinear directions of the diffusion sensitizing gradients was 30 for the MS sample and corresponding HC, while 61 for the M-BD sample and corresponding HC: this difference can be considered acceptable and uninfluential in the classic DTI metrics analysis, according to previous work (Giannelli et al., 2009; Jones, 2004; Landman et al., 2007). In addition, two sagittal volumetric images were obtained for all the subjects: a structural T1 weighted 3D-FSPGR (TR/TE = 9.6/4 ms, inversion time 500 ms, NEX = 1, in-plane matrix 256 × 256, FOV = 240 mm, slice thickness 1.2 mm with no gap) and a FLAIR-CUBE (TR/TE = 6000/129 ms, inversion time = 1856 ms, NEX = 1, in-plane matrix 256 × 256, FOV = 240 mm, slice thickness 1.2 mm with no gap). These two last scans were both reviewed by a board-certified neuroradiologist. No occasional findings and/or neurological comorbidities in the whole cohort, as well as significant WM lesions in the psychiatric and HC groups, were found, so that none of the subjects was excluded from the study.

2.3. Diffusion tensor imaging processing

A standard preprocessing was run on the DTI series from all subjects, featuring eddy current geometric compensation, brain extraction and fitting of the diffusion tensor, using tools from the Oxford University Centre for FMRIB software library (FSL 5.0, http://www.fmrib.ox.ac.uk/fsl/) (Smith, 2002; Smith et al., 2006; Smith et al., 2004; Woolrich et al., 2009). Diffusion tensor parametric maps were generated for FA, MD and RD. The obtained maps were all non-linearly co-registered on the standard FMRIB58_FA template of FSL, via standard tract-based spatial statistics (TBSS) pre-processing (Smith et al., 2006), to achieve an overlap of the WM tracts between all subjects. An *a-priori* region-of-interest (ROI) analysis was conducted. Specifically,