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SREBF-2 polymorphism influences white matter microstructure in bipolar disorder

Sara Poletti[a,b,*], Veronica Aggio[a], Irene Bollettini[a,b,c], Andrea Falini[b,d], Cristina Colombo[a], Francesco Benedetti[a,b]

[a] Scientific Institute and University Vita-Salute San Raffaele, Department of Clinical Neurosciences, Milan, Italy
[b] C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo), University Vita-Salute San Raffaele, Milan, Italy
[c] PhD program in Philosophy and Sciences of Mind; University Vita-Salute San Raffaele, Milan, Italy
[d] Scientific Institute and University Vita-Salute San Raffaele, Department of Neuroradiology, Milan, Italy

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ABSTRACT

The aim of the study is to investigate if gene polymorphisms in sterol regulatory element binding protein transcriptional factors SREBF-1 and SREBF-2, which regulate lipid and cholesterol metabolism, could affect white matter (WM) microstructure, the most recognized structural biomarker of bipolar disorder (BD). In a sample of 93 patients affected by BD, we investigated the effect of SREBF-1 rs11868035, and SREBF-2 rs1052717, on WM microstructure, using diffusion tensor imaging and tract-based spatial statistics. We observed increased radial diffusivity in the rs1052717 A/A genotype compared to A/G and G/G, and reduced fractional anisotropy (FA) in the rs1052717 A/A genotype compared to G carriers in cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation. These results seem to suggest an involvement of SREBF-2 in the integrity of white matter tracts in BD and therefore a possible role of SREBP pathway in CNS myelination processes.

1. Introduction

Bipolar disorder (BD) is a multifactorial disorder with a strong biological underpinning, characterized by the recurrence of depressive and manic episodes. One of the most recognized neurostructural markers of BD consists in widespread changes in white matter (WM) microstructure, involving all main WM tracts, and possibly contributing to the cognitive and emotional deficits of this disorder (Benedetti and Bollettini, 2014a; Nortje et al., 2013; Vederine et al., 2011). Diffusion tensor imaging (DTI) studies investigate the integrity of WM by assessing the diffusion properties of water molecules in brain tissues. Myelin sheaths envelop cells axons and force water diffusion along the main axis of the fiber, determining a preferential direction. Axial diffusivity (AD) represents the water diffusivity parallel to the axonal fibres, reflecting axonal integrity (Song et al., 2002). At the opposite, radial diffusivity (RD) is the mean of the diffusion along the two axis perpendicular to the axonal fiber, generally reflecting demyelination/re-myelination processes. The mean of the three diffusion eigenvalues constitutes the mean diffusivity (MD) index. Fractional anisotropy (FA) is the most used DTI index, and reflects the degree of anisotropic diffusion within a voxel, generally reflecting the myelination and the coherence of WM tracts (Vederine et al., 2011). Myelinated axons are one of the principal components of WM, and their ability in transmitting electric signals largely depends on the integrity of myelin sheaths that upholster axons, allowing an electrical insulation fundamental for efficient saltatory impulse conduction (Saher et al., 2005). In the central nervous system (CNS), myelin is composed for the 73–81% of its dry weight by lipids, and for the remaining 19–27% by proteins (Aggarwal et al., 2011). Lipids are fundamental not only for the synthesis of myelin, but also for its maintenance during lifespan (Schmitt et al., 2014). One of the principal lipids constituting myelin is cholesterol (Morell, 1984). In the CNS cholesterol is produced ex novo, because the circulating cholesterol cannot cross the blood brain barrier (BBB) (Dietschy and Turley, 2004). The biosynthesis of cholesterol and fatty acid is regulated by two different Sterol Regulatory Element-Binding Protein (SREBP) isoforms: cholesterol biosynthesis is mainly regulated by SREBP2, whereas the expression of fatty acid, triglyceride and phospholipid is controlled by SREBP1 (Le Hellard et al., 2010). The transcription of these factors depend on the Sterol Regulatory Element-Binding Transcription Factors (SREBFs) –1 and –2.

SREBFs have then been considered a new class of candidate genes

* Correspondence to: Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy.
E-mail address: poletti.sara@hsr.it (S. Poletti).

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in schizophrenia, and strong associations between SNPs covering the "lipogenesis-controlling" SREBF-1 and SREBF-2 genes and schizophrenia have been reported in large samples (Condra et al., 2007; Le Hellard et al., 2010).

For SREBF-1, we studied rs11868035, a C > T (reverse strand) or G > A (forward strand) SNP located in the intervening sequence next to the splicing site between exon 18c and 19c (IVS18c-3C > T), which has been associated with type 2 diabetes (Harding et al., 2006) and with Parkinson's disease (Do et al., 2011). rs11868035 is directly adjacent to the acceptor splice site for the C-terminal exon of the SREBP-1c isoform of the protein, suggesting a functional effect related to the splicing machinery (Do et al., 2011). The rs11868035 G/G genotype was associated with schizophrenia (Le Hellard et al., 2010). For SREBF-2, we studied rs1052717, a G > A SNP at nucleotide +414 of intron 11 (IVS11+414G > A) which has been associated with avascular necrosis (Kim et al., 2008) and with schizophrenia (Le Hellard et al., 2010). A previous study from our group investigated the effect of SREBF genes on DTI measures of WM integrity in schizophrenia showing an opposite effect of SREBF-1 and APDs on DTI measures suggesting shared mechanisms that can partly explain the changes of WM microstructure observed in this disorder (Bollettini et al., 2015).

WM abnormalities are not a specific characteristic of schizophrenia and have been widely reported also in BD and have been shown to be a shared characteristic of these illnesses (Anderson et al., 2013; Hercher et al., 2014). A recent study reported reduced myelin content in both disorders suggesting that WM abnormalities could be partly explained by changes in myelin content (Lewandowski et al., 2015). Because of an important role of cholesterol in myelin constitution we hypothesize that the influence of SREBF genetic polymorphisms on WM integrity observed in schizophrenia could be observed also in BD. We tested this hypothesis in a homogeneous sample of patients with BD.

2. Methods

2.1. Participants

We studied 93 biologically unrelated patients (31 males and 62 female) with a diagnosis of Bipolar Disorder Type I (Diagnostic and Statistical Manual of Mental Disorder, 4th edition TR - DSM-IV-TR), consecutively admitted at the psychiatric ward of San Raffaele Turro Hospital in Milan. Thirty patients (32%) were taking lithium from at least 6 months, 25 patients (27%) were taking antipsychotics with a mean Chlorpromazine equivalent dose of 65,38 ± 163,48, 32 patients (34%) were taking SSRI, 8 patients (8%) were taking SNRI and 15 patients (14%) were taking tricyclic antidepressant. Inclusion criteria were: absence of other diagnoses on Axis I, absence of major medical and neurological disorders, absence of previous history of relevant substance or alcohol abuse or dependency. BD type I diagnosis was made by trained psychiatrists using the SCID-I interview. Severity of depressive symptoms was rated on the 21-item Hamilton Depression Rating Scale (HDRS). After complete description of the study to the subjects, a written informed consent was obtained. The study protocol was approved by the local ethical committee.

2.2. Image acquisition

DTI was performed on a 3.0 T 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 2.14×2.71×2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88×1.87 mm; SENSE acceleration factor=2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value=900 s/mm2. 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 mm2 field of view) were acquired to rule out brain lesions.

2.3. Genotyping

DNA was manually extracted from whole blood, using the "Illustra blood genomic Prep Midi Flow kit" (GE Healthcare, Milan, Italy). To identify the single nucleotide polymorphism G/A rs11868035, a standard Polymerase Chain Reaction (PCR) was performed with the following primers: 5'- GAGGAGGCTTCTTTGCTGTG -3' and 5'- GGGTCAGTTGTCCCTTCTCA -3'. Instead for the identification of the single nucleotide polymorphism A/G rs1052717, a standard Polymerase Chain Reaction (PCR) was performed with the following primers: 5'- CATTTTGGTCCCCTGAGGTA -3' and 5'- TCGTCTGACCTGAGCTCCTT-3'. The PCR was carried out in a 10 µl volume containing 150 ng genomic DNA, 1 µl of 1× Hot Master Taq Buffer with Mg++(Eppendorf), 0.1 µl of each primer [50 µm], 1 µl of dNTPs [200 µm], 0.1 µl of Hot Master Taq [5 U/µl] (Eppendorf) and 0.5 µl of Dimethyl sulfoxide (DMSO). After an initial step of 3 min at 94 °C, 35 cycles of amplification (30 s at 94 °C, 30 s at 57 °C, 30 s at 70 °C) and a final extension step of 6 min at 70 °C were performed. The amplified fragment was then purified by Multi-Screen Colum Loader (MILLIPORE), filled up and packaged with Sephadex G-50 (Sigma-Aldrich's) to remove residual PCR reagents. An aliquot of purified PCR product was then used to perform sequencing reaction, using DYEnamic ET Dye Terminator Cycle Sequencing Kit (GE Healthcare, Milan, Italy). In its turn, sequencing reaction product, was purified following the abovementioned protocol, to remove the excess of fluorescent dyes not incorporated in the DNA fragment and then loaded onto a 48 capillaries genetic analyser (MegaBace 500, GE Healthcare, Milan, Italy).

2.4. Data processing and analysis

DTI analysis and tensor calculations were done using the "Oxford Center 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 vol 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. After removal of non-brain tissue (Smith, 2002), least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps. MD was defined as the mean of all three eigenvalues $[(\lambda_1 + \lambda_2 + \lambda_3)/3]$, AD as the principal diffusion eigenvalue (λ_1), and RD as the mean of the second and third eigenvalues $[(\lambda_2 + \lambda_3)/2]$.

Next, all individuals' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (Smith et al., 2006, 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html) and normalized to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (www.fmrib.ox.ac.uk/fsl/fnirt/index.html), a nonlinear registration toolkit using a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centres of all common tracts. We thresholded and binarized the mean skeleton at FA > 0.20 to reduce the likelihood of partial voluming in the borders between tissue classes. Individual FA values were warped onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. The resulting tract invariant skeletons for each participant were fed into voxelwise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD, and RD data sampled from voxels

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