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Special review article

Association of increased genotypes risk for bipolar disorder with brain white matter integrity investigated with tract-based spatial statistics

Special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summarise relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders.

L. Squarcina[a], J. Houenou[b,c], A.C. Altamura[d], J. Soares[e], P. Brambilla[d,f,*,1,2,3]

[a] IRCCS "E. Medea" Scientific Institute, Bosisio Parini, Italy
[b] APHP, Hôpitaux Universitaires Mondor, Pôle de psychiatrie, Faculté de Médecine, Université Paris Est, INSERM U955, IMRB, Equipe 15, Psychiatrie Translationnelle, Créteil, France
[c] UNIACT, Psychiatry Team, Neurospin Neuroimaging Platform, CEA Saclay, Gif-Sur-Yvette, France
[d] Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
[e] Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, USA
[f] Department of Psychiatry and Behavioural Neurosciences, University of Texas at Houston, TX, USA

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ABSTRACT

Background: Diffusion tensor imaging (DTI) studies, which allow the in-vivo investigation of brain tissue integrity, have shown that bipolar disorder (BD) patients present signs of white matter dysconnectivity. In parallel, genome-wide association studies (GWAS) identified several risk genetic variants for BD. I

Methods: In this mini-review, we summarized DTI studies coupling tract-based spatial statistics (TBSS), a reliable technique exploring white matter axon bundles, and genetics in BD. We performed a bibliographic search on PUBMED, using the search terms "TBSS", "genetics", "genome", "genes", "polymorphism", "bipolar disorder".

Results: Ten studies met these inclusion criteria. ANK3 and ZNF804A polymorphisms have shown the most consistent results, with the risk alleles showing abnormal white matter integrity in patients with BD.

Limitations: Current studies are limited by the investigation of single SNPs in small and chronically treated samples.

Conclusions: Most considered TBSS-DTI studies found associations between decreased white matter integrity and genetic risk variants. These results suggest an involvement of dysmyelination in the pathogenesis of BD. The combination of TBSS with genotyping can be powerful to unveil the role of white matter in BD, in conjunction with risk genes. Future DTI studies should combine TBSS and GWAS in large populations of drug-free or minimally treated patients with BD at the onset of the disease.

It has been shown that Bipolar disorder (BD) has an impact on brain gray and white matter structure and integrity (Houenou et al., 2012; Wise et al., 2016). Particularly, current models stress out the importance of dysconnectivity in the pathophysiology of BD (Phillips and Swartz, 2014), which can be in vivo non-invasively investigated by diffusion tensor imaging (DTI). Diffusion indexes indeed give a measure of tissue integrity. The most widely studied is fractional anisotropy (FA), which is higher when water movement is constrained, e.g. in

* Correspondence to: Dipartimento di Neuroscienze e Salute Mentale, U.O.C. Psichiatria (Pad. Alfieri), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milan, Italy.
E-mail address: paolo.brambilla1@unimi.it (P. Brambilla).
[1] Associate Professor of Psychiatry, University of Milan, Milan, Italy.
[2] Adjunct Associate Professor of Psychiatry, University of Texas at Houston, USA.
[3] Chair, EPA Neuroimaging Section.

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packed and well organized white matter; thus, its decrease could be a sign of structural connectivity disruption. Mean diffusivity (MD) quantifies the amount of diffusion inside a voxel, which is higher for less organized tissues, i.e. MD is higher for cerebral-spinal fluid than for gray matter. Radial diffusivity (RD) and axial diffusivity (AD) measure the diffusion perpendicularly and along the main diffusion direction, respectively; in particular, an increase in RD could reflect demyelination. In this perspective, tract-based spatial statistics (TBSS, Smith et al., 2006) allows the exploration of these parameters in major white matter bundles using a dedicated framework, with strong advantages over more classical analyses techniques not dedicated to DTI, by reducing the possibility of errors due to subject movement or misregistration. TBSS-DTI studies, which investigate specifically white matter axon bundles, reported signs of demyelination and reduced bundle coherence in BD (Bellani et al., 2011, 2016). Specifically, they consistently found reduced fractional anisotropy (FA) and elevated radial diffusivity (RD) and mean diffusivity (MD), which suggest processes of dysmyelination (Bellani et al., 2009; Benedetti et al., 2011).

The pathophysiology of BD is to date not entirely clear. It is likely that it stems from a combination of genetic and environmental factors (Kieseppä et al., 2004). After the recent complete mapping of the human genome, genome-wide association studies (GWAS) identified several risk genetic variants for BD. The most consistent results were obtained when investigating genes CACNA1C, which is involved in the calcium cellular channel processes (Gurung and Prata, 2015), ANK3, involved in neurogenesis and in maintaining axonal structure on brain integrity (Linke et al., 2012), and ZNF804A, which encodes a zinc finger protein, involved in neurodevelopment and myelin transcription (Gurung and Prata, 2015). However, full knowledge of the role of the majority of genes found in GWAS in BD pathogenesis is lacking, thus making the interpretation of results, and particularly their application to the clinic, very difficult (Prata et al., 2014).

The association of genetics with the analysis of cerebral tissue integrity in patients with BD could be of high relevance to better understand how they increase the liability to the disease. In this selective review, we selected studies which investigated white matter, using TBSS, in conjunction with analysis of polymorphisms. A bibliographic search on PUBMED was performed using the search terms “TBSS”, “genetics”, “genome”, “genes”, “polymorphism”, “bipolar disorder”. Ten studies, which have been summarized in Table 1, met these inclusion criteria. We excluded studies employing techniques different from DTI-TBSS for the investigation of white matter structure.

Sprooten et al. (2011) studied the effects of the gene DISC1, whose variants are known to be risk factor for psychiatric disorders, including BD, on FA of white matter of healthy volunteers. They found that the rs821616 risk allele (A) was associated with lower FA in most white matter tracts, both in homozygotes for the allele and in carriers. Moreover, homozygous showed lower FA in the right superior fasciculus than carriers. This supports the potential link between the increased risk for BD given by DISC1 genotypes and the development of the disease mediated by decreased integrity of white matter.

In a later work, the same group (Sprooten et al., 2012) took into account three different groups of healthy volunteers, one of which composed by unaffected relatives of BD patients. The comparison between the ZNF804A risk-allele A homozygous and the non-risk-allele (C) carriers gave no significant results. In contrast, Ikuta et al. (2014) found an association between lower FA and the risk allele in corpus callosum, left forceps minor and left parietal lobe in healthy individuals. Interestingly, they did not divide their sample in homozygotes and carriers, but considered A allele “dosage” ranging from 0 to 2. A higher risk-allele dosage was associated with lower FA. A correlation was also found between higher RD and higher allele dosage, possibly indicating that the tissue differences are related with myelination, consistently with the role of the ZNF804A gene. A recent study (Mallas et al., 2016b) also found decreased FA in A-homozygous in respect to C carriers in various parts of the brain, including corpus callosum, longitudinal fasciculus, corona radiata, internal and external capsula, in healthy controls, BD patients and SCZ patients when considered all together independently of the diagnosis. These findings support the association between the risk allele and the reduced interhemispheric connectivity, mediated by structural modifications.

In another work, Mallas et al. (2016a) considered the risk allele of CACNA1C gene in healthy controls and patients with BD and SCZ who also had data for ZNF804A genotype. They found a relationship between the presence of the CACNA1C allele risk and FA only in schizophrenia, but neither considering BD and healthy controls separately, nor considering all subjects together. A three-way interaction between ZNF804A and CACNA1C genotypes and diagnosis was found, but it was not significant after correction for age differences. Thus, the authors suggest a minor association of CACNA1C with brain microstructure related to psychosis, while the influence of diagnosis or ZNF804A genotype on FA was stronger. Linke and colleagues (2012) considered the rs10994336 and rs9804190 ANK3 risk variants, and found decreased FA and AD in the right anterior limb of external capsule in rs10994336 healthy risk allele carriers. Then, they concluded that white matter could be an intermediate phenotype related to the single nucleotide polymorphism rs10994336. Also Ota and colleagues (2016) investigated the risk variants of ANK3. They found decreased FA in the right forceps minor in patients with BD homozygous for the rs10761482 risk allele (C), and no effects in healthy controls. These results point to an involvement of ANK3 genotype in neurodegeneration and possibly in BD pathogenesis.

Benedetti and colleagues investigated, in two distinct studies on two different samples, the influence of the variants of promoters of Glycogen synthase kinase 3-β (GSK3-β) and of serotonin transporter 5-HTT (5-HTTLPR) on white matter structure in BD patients. The authors (Benedetti et al., 2013) found increased AD and MD in most of the white matter tracts of patients carriers of the less active C variant of GSK3-β rs334558. This gene has a role in neurodevelopment and neural plasticity, and the low-activity allele of its promoter has been associated with less symptom severity in mood disorders (Benedetti et al., 2004). Successively, Benedetti et al. (2015) showed increased MD and RD in many white matter bundles, including corpus callosum and longitudinal fasciculus, in carriers of the short allele of the 5-HTTLPR with BD. It has been demonstrated that 5-HTTLPR is associated with worse response to antidepressant (Smeraldi et al., 1998; Zanardi et al., 2000) and emotional deficits (Pezawas et al., 2005). The results of Benedetti and colleagues suggests a role of white matter alterations in mediating the effects of 5-HTTLPR on affective processing.

In conclusion, the majority of the considered TBSS-DTI studies found associations between decreased white matter integrity and genetic risk variants, suggesting the potential involvement of dysmyelination processes in the pathogenesis of BD (Brambilla et al., 2004, 2009).

For this work, we selected only DTI-TBSS studies for our review, disregarding non-TBSS DTI studies or studies investigating structural integrity with other acquisition techniques: this clearly limits the inclusiveness of our results. Nonetheless, we believe that restricting our review to DTI-TBSS studies favours clarity and consistency.

In general, the combination of TBSS with genotyping can be considered a powerful approach for exploring the role of white matter in mediating the effects of risk genes to BD. It has to be noted that some studies find associations with genetic variations only in some subgroups of patients (Mallas et al., 2016; Ota et al., 2016; Benedetti et al., 2013, 2015; Poletti et al., 2016): these results are particularly significant because, if patients are homogeneous as regards medication and symptoms, such differences could elucidate the role of genotypic variations in BD.

However, current studies are still limited by the investigation of single SNPs in small sample size including mostly chronically treated patients. In fact, the consideration of single polymorphisms could lead to bias in this field. Future studies should carefully evaluate this risk,