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BIPOLAR DISORDER (J SOARES AND M SANCHES, SECTION EDITORS)

A Critical Review on Structural Neuroimaging Studies in BD: a Transdiagnostic Perspective from Psychosis to Fronto-Temporal Dementia

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Abstract

Recent Findings In the last decades, many neuroimaging studies have investigated the brain structural deficits associated with the pathophysiology of Bipolar Disorder (BD). Notably, the available literature identified the presence of selective brain structural abnormalities, in terms of both gray matter (GM) and white matter, known to be involved in emotion regulation and processing. Nonetheless, the complex and heterogeneous nature of BD has not yet allowed the identification of a clear biological signature of this disorder.

Purpose of Review In this context, this review aims to a) briefly summarize the evidence from structural Magnetic Resonance Imaging (MRI) studies on BD in order to provide a clearer picture of the neural circuits involved in this disabling mental illness, and b) describe some critical clinical issues that need to be taken into account when studying BD, especially the history of psychosis and the link between BD and behavioral variant fronto-temporal dementia (bvFTD).

Summary Evidence from structural MRI studies on BD suggests ventricular, prefrontal and temporal abnormalities but remain largely inconsistent, possibly reflecting the disorder complexity. Moreover, the reviewed evidence showed that psychotic BD might represent a subtype of the disorder with specific and enhanced alterations of GM morphology. Finally, from the available MRI evidence exploring the relationship between BD and bvFTD emerged the need of a differential identification of biological markers to enable the early and accurate detection of the two disorders, ultimately guaranteeing a better prognosis and the employment of more targeted and effective treatments.

Keywords Bipolar disorder · Magnetic resonance imaging · Psychosis · Behavioral variant fronto-temporal dementia · Gray matter · White matter

This article is part of the Topical Collection on *Bipolar Disorder*

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Introduction

Bipolar Disorder (BD) is a chronic and recurrent psychiatric illness characterized by mood fluctuation, ranging from severe depression to extreme euphoria, known as episodes of mania, which have a negative impact on quality of life and are associated with high levels of disability and mortality [1]. BD is a disease that transitioned between states, possibly due to a disruption in brain activity, which could normalize after the implementation of pharmacological treatments [2]. Moreover, BD is a complex disease that derives from the interaction of a genetic susceptibility, still not entirely determined, with biological, psychological and environmental factors. Importantly, it has been also consistently suggested that this disorder shows state- and trait-related cognitive and emotional deficits, especially in attention, executive functions, and

emotional processing, that further exacerbate its clinical profile [3]. Interestingly, these deficits are present during the mood episodes and during euthymia [3, 4]. Moreover, since BD is a brain-based disorder, in the last decades, the scientific community has tried to identify the potential biomarkers associated with BD phenotype, through Magnetic Resonance Imaging (MRI) approaches, with the final aim of increasing the knowledge on the pathophysiology of the disease. Indeed, non-invasive neuroimaging methods enable the investigation of brain structure, connectivity and function with high accuracy, ultimately making it feasible to identify biological underpinnings of mental disorders. This is of paramount importance since the discovery of selective biomarkers associated with a specific disorder might be translated into clinical use, especially for early diagnosis and intervention as well as for the identification of more effective and targeted pharmacological treatments.

The clinical heterogeneity of BD represents a major obstacle in the search for the neurobiological bases of this complex disorder. Although a neural circuit that includes prefrontal regions, including dorso- and ventro-lateral prefrontal cortices (PFC), and subcortical areas, including amygdala, hippocampus and ventral striatum, seems to play a key role in the pathophysiology of the disorder, especially because these structures are involved in the processing and regulation of emotional stimuli [5, 6, 7••, 8], the results are still far to be conclusive.

However, we are still far from the identification of selective biomarkers specifically associated with BD for mainly two reasons, one methodological and one clinical. First, the available MRI studies employed a variety of methodological approaches (e.g., different MRI scanners, voxel-based vs. region-based approaches, different statistical significance thresholds) that determine difficulties in comparing the evidence between studies and resulted in heterogeneous findings. Second, BD shares clinical symptoms and neurobiological aspects with other psychiatric disorders and it has a heterogeneous nature in terms of its clinical presentation, ultimately challenging the identification of specific brain abnormalities associated with the disorder. Therefore, in recent years, international collaborations for the study of BD (for example, the ENIGMA BD working group and the European Network on Psychosis, Affective disorders and Cognitive Trajectory [ENPACT] network) were formed in order to identify brain structural deficits that may consistently differentiate BD patients from healthy individuals [7••, 8, 9] and schizophrenia patients [9]. Although the ENIGMA results represent the most robust evidence on structural brain differences in BD compared to healthy subjects, their reliability might still be affected by the several sources of heterogeneity within the analyzed dataset, concerning both acquisition protocols and patient characteristics. A more reliable knowledge might be obtained by accounting for the non-unitary entity of this disorder in the framework of the Research Domain Criteria (RDoC) [10].

In this context, the main aims of this critical review are threefold. First, we provide an overview of gray matter (GM) and white matter (WM) alterations associated with BD in order to explore the biological underpinning of BD. Second, by adopting a dimensional perspective, we describe the impact of psychosis on GM volumes and its role in exacerbating the BD clinical phenotype. Finally, we aim at elucidating the complex relationship between dementia and primary psychiatric illnesses, since it is still a neglected area of interest. Specifically, we describe the common and distinct brain structural abnormalities associated with elderly BD patients and behavioral variant frontotemporal dementia (bvFTD) reported by the available MRI studies.

Structural Brain Abnormalities in Bipolar Disorder: Main Findings from T_1-Weighted and DTI Studies

Many studies investigated brain morphology in BD using structural MRI, and in particular T_1-weighted MRI Imaging. This technique is particularly sensitive to structural details and allows a precise quantification of GM and WM structures. After more than three decades since the first MRI studies on BD [11], despite the numerous efforts being made, the results continue to be somewhat discordant. Indeed, mixed findings concerning cortical and subcortical structures have emerged, which could be explained considering differences in the study protocols and methodology, the clinical heterogeneity of BD patients, in terms of symptoms, illness severity and mood phase, and, importantly, the employment of small sample sizes.

Notably, the most consistent result in structural T_1-weighted imaging is an enlargement of ventricular volumes [12, 13], which was also confirmed by meta- and mega-analyses [8, 11, 14]. However, the diagnostic specificity of the emerged ventricular enlargement may be disputed. In fact, ventricular enlargement is common to other disorders, such as schizophrenia and depression [15], therefore suggesting that this alteration may not be a specific marker of BD.

Many structural MRI studies on BD focused their attention towards the investigation of brain regions that are part of the limbic circuitry, including hippocampus and amygdala, mainly due to their pivotal role in emotion regulation and mood modulation. However, also in this case, the results are often conflicting [2, 16]. In fact, while some studies reported significant hippocampal GM reductions in BD [8, 17], also mimicking accelerated aging [18], other meta-analyses and independent MRI studies did not find any significant differences [9, 13, 14]. This seems to be true also for the amygdala, with meta- or mega- analyses showing no differences between BD

patients and controls [13, 14,19] while other studies reporting either an enlargement [20] or a reduction [8, 21, 22] of this structure. Importantly, it has been also demonstrated that these brain regions seem to be more sensitive to neuroprotective effect of lithium [14, 21], thus it is reasonable to assume that the effects of the disease may be reduced, or at least confounded, by lithium.

Moreover, several studies focused on GM thickness or shape, obtaining very heterogeneous results in terms of both the regions involved and the directions of these modifications [7••]. For example, differences in respect to controls have been identified in the hippocampus [23, 24] and in the cortical folding of structures of the limbic network, in particular the thalamic circuit and the anterior cingulate cortex [25]. Moreover, specific modifications of cortical folding have been found in both psychotic and early onset BD patients in the prefrontal cortex and in the parietal cortex respectively [26]. Also, WM shape seems to be affected by BD, for example in the cingulum, in the uncinate and arcuate fasciculi [27]. Regarding cortical thickness, many studies reported the presence of thinning in the left anterior cingulate and paracingulate regions, the left superior temporal gyrus, and some bilateral prefrontal regions [28]. Notably, these findings have been partially confirmed by the biggest analysis carried out by the ENIGMA-Bipolar Disorder Working Group [7••] with a sample of more than 2400 BD patients and 4000 healthy controls. However, also in this case, these findings are not distinctive of BD but can be found also in other psychiatric disorders, e.g., schizophrenia [29, 30], suggesting a possible overlap in their pathogenesis.

In the last decade a major interest for the role of WM in the pathophysiology of BD has grown, as WM constitutes the brain's connective wiring, with increasing evidence suggesting the key role exerted by WM abnormalities in BD [31]. Diffusion tensor imaging (DTI) allows the investigation of WM, thanks to the property of water to diffuse in an anisotropic way in fiber bundles, as opposed to the isotropic diffusion occurring in water and, to a lesser extent, in GM. The most straightforward method to analyze DTI data is to fit them to a three-dimensional tensor, which models the diffusion process. Changes in diffusion reflect modifications in tissue integrity: trauma, demyelination or Wallerian degeneration result in modified water diffusion. For example, the myelin disruption underlying Wallerian degeneration leads to a reduction in Fractional Anisotropy (FA), which describes the degree of anisotropy of a tissue, caused by a decrease of diffusion parallel to the fiber and an increase of perpendicular diffusion [32]. Other DTI indexes of interest are mean diffusivity (MD), which describes the intensity of water diffusion, and axial and radial diffusivity, which measure the amount of diffusion that occurs along the principal axis of the diffusion tensor and perpendicularly to it, respectively [33].

Although a certain degree of heterogeneity persists also for diffusion studies, DTI indexes have been found to be altered in all major WM structures and bundles in BD [34•]. Region of interest (ROI) – level analyses revealed an association of BD with a disruption of tissue integrity, as demonstrated by a decrease in FA and an increase in MD, especially in prefrontal and frontal tracts [35–38], corpus callosum [39–41] and limbic structures [37, 39]. Notably, a whole-brain and tractography study also confirmed the presence of widespread WM deficits in BD [42]. Nonetheless, similarly to what have been stated for the T_1-weighted-based findings, it is difficult to pinpoint a specific biomarker for BD, as it shares not only symptoms but also neurobiological aspects with other disorders, including schizophrenia [43, 44] and unipolar depression [45, 46]. Importantly, it has been suggested that medication with mood stabilizers exerts a neuroprotective effect on tissue integrity, with some studies reporting increased FA in frontal, parietal, temporal and occipital areas [47, 48], suggesting an increased coherence of fibers during remission or induced by medication. Finally, Magioncalda et al. (2016) [49] observed a degree of microstructure alteration related with the phase of BD, with a gradient of disruption from the euthymic to the depressive phase. The relation of specific phases of BD with microstructure has, to date, been scarcely investigated, and more studies are needed to identify the possible impact of the disorder's phase on tissue integrity.

The use of the tensor model, which is the model used by the vast majority of diffusion studies, has the advantage of mathematical simplicity, which leads to a certain ease of interpreting results. On the other hand, this model provides only a limited set of parameters to be investigated, none of which can truly directly measure WM integrity [50•]. Recently, alternative models for the study of diffusion data have been proposed. Pasternak et al. (2018) [50•] identified several advanced methods of analysis that have been applied to BD. Some of these methods require the definition of models, which for example identify multiple compartments, as neurite orientation dispersion and density imaging (NODDI). Others do not require models and rely on the properties of the signal itself, as diffusion spectral imaging (DSI) or diffusion kurtosis imaging (DKI). These methods usually require non-standard diffusion acquisitions that may be difficult to obtain in clinical settings, due to the exams' duration and technical difficulties, so the number of studies applying these techniques to patients is still small. Amongst the model-based techniques, it is worth mentioning the study by Tuozzo et al. (2018) [51] where BD patients were found having increases in free water, represented as a second compartment, that the authors interpreted as related to acute response, possibly inflammation. The NODDI model accounts for three compartments (intracellular, extracellular and free water), and was used by Nazeri et al. (2017) [52] for the study of diffusion in BD, but they found no differences between BD and healthy controls in

any compartment. Interestingly, Sarrazin et al. (2019) [53] used the same method to investigate GM neurite density in medicated and not-medicated BD patients, and found that patients using lithium had higher neurite density than non-medicated patients, who, in turn, had lower neurite density also than controls, adding to the evidence that lithium has a neuroprotective effect on brain tissue. DSI is based on a denser acquisition of diffusion data than standard. Generalized FA (gFA) is a diffusion index that can be derived with this technique: it is similar to FA, but more directly linked with fiber anisotropy, and more reliable in case of complicated fiber architecture. Interestingly, by using this method, four studies reported similar results and specifically a decreased gFA in various WM tracts, including the corpus callosum, insula and cingulum in BD patients compared to healthy controls [54–57]. In contrast, Favre et al. (2016) [58] found no differences in any WM tracts between BD patients and controls. Finally, the advanced technique for analysis of diffusion data which is most used in clinical settings, although it is still scarcely used for psychiatric disorders, is the DKI [50•], which is a model-free method that reflects the restricted water diffusion. Notably, recent studies employed this model and showed lower mean kurtosis and neurite density in BD patients when compared to controls, especially in right inferior front-occipital fasciculus, right posterior cingulate cortex, cerebellum and caudate, reflecting a loss of microstructural integrity and complexity [59, 60].

In conclusion, although the application of these methodologies is still at its infancy, the use of more complex models for diffusion data or the avoidance of strong a-priori hypotheses may allow the study of diffusion profiles also in non-homogeneous WM areas where fibers have complex architectures, or even in GM regions, and may help to achieve a better specificity than conventional DTI analyses.

The Impact of Psychosis on Brain Abnormalities in BD Patients

As can be seen from the previous section, the identification of the brain structural signatures of BD is still at the beginning. The lack of certain knowledge might be related to the categorical perspective adopted by most studies, which compared BD patients to healthy subjects without considering possible associations between clinical symptoms and brain morphology within the broad BD spectrum. Recent advancements in the conceptualization of BD have been brought by the DSM-5, which specifies more sub-diagnostic categories with an improved dimensional approach to severity [61].

On the contrary, the adoption of a dimensional approach might unveil biologically determined dimensions with a strong impact on the disease trajectory. In the described scenario, a relevant clinical dimension is psychosis, which is expressed in more than one half of BD type I patients [62] and in a lower, but non-negligible, proportion of BD type II patients [63]. Psychotic features were found to be associated with earlier age of disease onset, more frequent hospitalizations for manic episodes [62], enhanced cognitive dysfunction [64], worse sociodemographic and clinical profile [65] and poorer functional outcome [66, 67].

Psychosis has recently been proposed as a shared transdiagnostic dimension encompassing BD, schizoaffective disorder and schizophrenia [68]. This hypothesis is supported by the extensive genetic overlap between BD and schizophrenia - with 114 genome-wide loci contributing to both the disorders [69] - and by evidence of a significantly higher number of schizophrenia polygenic risk scores in BD with psychotic features compared to BD without psychotic features [69].

Thus, psychotic BD might represent a subtype of BD with specific genetic and neurobiological determinants that intersect the schizophrenia spectrum. This hypothesis is further acknowledged by evidence from a recent Positron Emission Tomography (PET) study, which found an elevated dopamine synthesis capacity in psychotic BD, to a degree similar to that observed in schizophrenia and proportional to psychotic symptom severity [70]. Of note, a previous molecular imaging study found unaltered dopamine function in non-psychotic manic BD patients compared to healthy controls [71], which suggests a direct link between high dopamine synthesis capacity and psychotic symptoms in BD.

Although structural MRI has been increasingly used to investigate the brain morphological overlap between BD and schizophrenia, a consensus on this topic has not been achieved. Recent multicentric studies provided evidence of wider GM deficits in schizophrenia than in BD in comparison with healthy subjects, with common deficits mainly in cingulate and temporal regions [9, 72]. Meta-analytic approaches confirmed the partial neuroanatomical overlap between the two disorders, albeit with more extensive deficits in schizophrenia [73, 74]. Nevertheless, most of these studies did not take into account the clinical heterogeneity in BD, leaving doubts on the nature and degree of the shared neuroanatomical determinants.

Therefore, the stratification of BD based on psychotic symptoms appears crucial to deepen our understanding of brain morphological markers of BD, also in relation with other mental illnesses. Up until now, just few research works directly compared BD individuals with vs. without psychotic symptoms in terms of GM structure, and evidence on the neuroanatomical similarity between the two BD subtypes remains limited. The available evidence on the impact of psychosis on GM volume in BD was recently reviewed by our group and by Wang et al. [75, 76]. Notably, many of these studies involved small BD samples, with less than 100 patients, or focused on a priori selected regions of interest [77–84]. To our knowledge, only three studies adopted an unbiased whole-

brain approach on wider samples of patients, using either voxel-based morphometry (VBM) [85, 86] or surface-based regional parameters [7••].

Notably, the largest study conducted by the ENIGMA BD working group [7••], suggested an evolution of cortical alterations linked to psychosis thorough life. The authors reported that during adolescence/young adulthood, BD patients with a history of psychosis had lower surface area in left inferior temporal gyrus and right caudal anterior cingulate cortex than their non-psychotic counterpart; conversely, during adulthood lifetime psychosis was associated with surface area deficits in the right frontal pole.

This evidence is partially in line with findings from voxel-based studies, suggesting a role of frontotemporal cortex in psychosis [82, 85, 86]. Of note, frontal abnormalities have been linked to psychoses from the prodromal stage, since we recently found altered perfusion indexes in bilateral frontal cortex in first-episode psychosis [87]. Furthermore, another recent study from our group showed lower frontal cortical complexity in both BD and schizophrenia [88]. Regarding the temporal cortex, its renowned involvement in major psychoses supports the hypothesis of dimensional continuity between BD and schizophrenia through the psychotic BD subtype [9, 72].

Importantly, it is worth mentioning that, so far, the two largest VBM studies found more severe volumetric deficits in psychotic BD patients than in non-psychotic ones when compared to healthy subjects, and agreed on the presence of right parietal deficits in BD patients with a history of psychosis compared to the other BD patients [85, 86]. In another VBM study, the right parietal cortex was found to be specifically involved in the most severe type of psychosis, characterized by mood incongruent features [78]. In a multi-center region-based investigation of cortical folding, patients with psychotic BD showed deficits in local sulcation index in left superior parietal cortex compared to non-psychotic ones [26]. Although no parietal deficits were linked to psychosis in the ENIGMA study, this discrepancy might be due to the methodological differences between surface-based and voxel-based techniques and does not necessarily indicate a lower reliability of the result.

Interestingly, the research works that compared psychotic and non-psychotic BD in terms of subcortical morphology reported no differences, with the exception of some reports of increased globus pallidus [80, 84] and caudate [77] in the psychotic group.

Although further confirmations are needed, the available evidence suggests that psychotic BD is characterized by more severe GM alterations than non-psychotic BD. This result is in line with knowledge of specific psychopathological correlates of the psychotic dimension, including earlier onset and worse prognosis, and supports the recently advanced hypothesis of specific developmental patterns, with enhanced neurodevelopmental insult in psychotic vs. non psychotic BD [26]. This subtype specific framework, in turn, might exacerbate the progressive decline in mental health, social functioning and cognitive performance that seems to accompany the course of the illness, according to the theory of neuroprogression [89].

Bipolar Disorder Vs Behavioral Variant Fronto-Temporal Dementia: Is there a Neurobiological Link?

Since BD has been considered a progressive condition with functional decline over time, in recent years, the scientific interest has also been driven towards the identification of common and distinct structural brain abnormalities associated with elderly BD and bvFTD, with the final aim of designing the clinical hallmarks of these diseases. This interest derived from the clinical evidence showing extensive symptomatic overlaps between these two disorders, ultimately suggesting the presence of a putative etiopathogenic link between BD and bvFTD.

Indeed, bvFTD is a neurodegenerative disorder characterized by a complex symptomatology, which includes behavioral, cognitive, personality and psychiatric symptoms, which may mimic the ones observed in BD patients [90]. In particular, bvFTD patients may show behavioral changes, including disinhibition, social inappropriateness, excessive jocularity, as well as mood disturbances, including euphoria and irritability, all symptoms that also characterize BD patients, especially during manic phases [91]. Therefore, it is not surprising that bvFTD is often misdiagnosed as BD, which in turn may delay the identification of correct treatments.

Similarly, numerous studies have consistently reported the presence of extensive cognitive deficits in BD patients, regardless of mood state, which seem to progressively increase with age [92, 93] without being associated with prodromal phases of dementia [93–95]. Interestingly, there is evidence of a relation between manic episodes and prevalence of dementia in elderly BD patients [96, 97], ultimately leading to the hypothesis that BD might be a risk factor for developing dementia [98].

Therefore, it is not surprising that in recent years the scientific interest has been driven towards the study of the molecular and biological pathways shared by these diseases. From a molecular point of view, it has been reported that FTD patients with psychiatric symptoms often were carriers of specific genetic mutations, primarily the hexanucleotide expansion in chromosome 9 (*C9ORF72*) [99, 100], which was also described in patients with psychotic symptoms [101], but, to a lesser extent, also microtubule-associated tau protein gene (*MAPT*) [102] and progranulin (*GRN*) genes [103]. Therefore, overall these findings suggest the need of

performing genetic analyses in order to clearly identify the genetic risk factors associated with the development of neurodegenerative and psychiatric disorders with the final aim of better delineating their molecular bases.

Similarly, from a biological prospective, the disambiguation of these two disorders is still far from being obtained, especially because there are no defined biomarkers, which are, though, important for increasing the discrimination power of clinicians during the diagnostic process. Although MRI and PET techniques have been proven very useful for discriminating bvFTD from other psychiatric disorders, their diagnostic accuracy is still debated [104]. Indeed, although the absence of fronto-temporal abnormalities and hypo-metabolism have been considered key predictors of a primary psychiatric illness versus bvFTD [105], a thorough clinical evaluation is still paramount for distinguishing the two diagnoses. This is because these techniques are rather sensitive, especially for PET, but still lack of specificity [104], ultimately suggesting the need to be cautious in interpreting the MRI /PET results.

Nonetheless, despite these limitations, from the available neuroimaging evidence on bvFTD and BD emerged that elderly BD and bvFTD show not only clinical similarities but also deficits in overlapping brain regions, especially in prefronto-temporal regions, ultimately suggesting the presence of shared brain disruptions. Specifically, for BD, evidence from large sample studies suggests significant GM reductions in ventro- and dorso-lateral PFC, anterior cingulate cortex as well as other cortico-limbic regions [7••, 8, 106, 107]. Similarly, the MRI evidence on bvFTD showed the presence of extensive GM abnormalities in cortical regions, including frontal, parietal and temporal cortices, as well as in subcortical structures, including striatum, amygdala and hippocampus [108–110].

Also, BD and bvFTD patients seem to share common WM alterations. Specifically, the most replicated findings in bvFTD were the alterations in corpus callosum, uncinate fasciculus, superior longitudinal fasciculus and anterior cingulate bundle [111–113]. Similarly, in BD, two recent VBM meta-analyses reported the presence of WM deficits in corpus callosum, posterior cingulum fibers, inferior longitudinal fasciculus, and superior corona radiata [114, 115]. Nonetheless, although there are many studies or case reports suggesting the presence of clinical similarities between bvFTD and elderly BD, only few MRI studies directly compared these two disorders. Indeed, only two recent studies [116, 117] explored the common and distinct brain abnormalities between elderly BD and bvFTD. Interestingly, both studies reported that bvFTD patients showed more extensive GM reductions in prefronto-temporal regions compared to BD. Moreover, Delvecchio et al. (2018) [117] also showed that GM reductions in prefrontal regions were localized in different areas, the ventrolateral portion for BD, also observed by Baez et al. (2017) [116], and the dorsolateral one for bvFTD. Finally, the two studies also reported unique alterations in the striatum in BD patients, including the caudate [117] and the putamen [116], as well as in temporo-parietal regions in bvFTD patients [117].

Therefore, the abovementioned results suggest that the shared symptomatology between BD and bvFTD may be explained by the presence of alterations within overlapping brain regions. Therefore, the differential identification of biological markers will enable the early and accurate detection of the two disorders, ultimately guaranteeing a better prognosis and the employment of more targeted and effective treatments.

Conclusions

In summary, evidence from structural MRI studies on BD suggests ventricular, prefrontal and temporal abnormalities but remains largely inconsistent, possibly reflecting the disorder complexity [7••, 8, 19, 118, 119]. Technical advances, especially in diffusion imaging techniques, might allow discerning the biological basis of the disease, facilitating the diagnostic and prognostic processes. However, the definition of a brain structural biomarker specific for BD does not seem a realistic objective, due to methodological limitations and similar patterns of structural disruption shared with other psychiatric conditions. Nevertheless, psychiatric neuroimaging is in constant evolution generating new cutting-edge neuroimaging methods enabling us to disentangle the neurobiological fundaments of BD.

Furthermore, it is important to mention the need to extend our understanding of the impact of clinical variables - including illness severity, mood phases, specific symptom dimensions (e.g., psychosis) - on brain morphology, since it is still limited. Indeed, the abovementioned evidence showed that psychotic BD might represent a subtype of the disorder with specific and enhanced alterations of GM morphology; the available knowledge of the structural abnormalities in psychotic BD compared to non-psychotic BD lets us hypothesize a role of frontal, temporal and parietal regions in the psychotic dimension that deserves further investigations. Therefore, a deeper understanding of the brain architecture underlying psychosis could increase the diagnostic and prognostic capability and provide significant benefits for personalized clinical management.

Finally, psychiatry neuroimaging might be a useful tool also for identifying endophenotypes to discriminate between BD and other psychiatric or neurological (e.g., bvFTD) disorders. The identification of specific biological signatures of the disorders may be crucial for enabling clinicians to have new insights in the diagnosis and treatment of these illnesses.

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Compliance with Ethical Standards

Conflict of Interest The authors have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1 Oswald P, Souery D, Kasper S, Lecrubier Y, Montgomery S, Wyckaert S, et al. Current issues in bipolar disorder: a critical review. Eur Neuropsychopharmacol. 2007 Nov;17(11):687–95.
2 Cousins DA, Grunze H. Interpreting magnetic resonance imaging findings in bipolar disorder. CNS Neurosci Ther. 2012;18:201–7.
3 Cipriani G, Danti S, Carlesi C, Cammisuli DM, Di Fiorino M. Bipolar disorder and cognitive dysfunction: a complex link. J Nerv Ment Dis. 2017 Oct;205(10):743–56.
4 Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004b;161:262–70.
5 Strakowski S, Delbello M, Adler C. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry. 2005;10:105.
6 Blond BN, Fredericks CA, Blumberg HP. Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala-anterior paralimbic neural system. Bipolar Disord. 2012;14:340–55.
7.•• Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA bipolar disorder working group. Mol psychiatry 2018;23(4):932-42. This is the largest study investigating brain structural abnormalities in bipolar disorder patients.
8. Hibar DP, Westlye LT, van Erp TG, Rasmussen J, Leonardo CD, Faskowitz J, et al. Subcortical volumetric abnormalities in bipolar disorder. Mol Psychiatry. 2016;21(12):1710–6.
9. Maggioni E, Crespo-Facorro B, Nenadic I, Benedetti F, Gaser C, Sauer H, et al. Common and distinct structural features of schizophrenia and bipolar disorder: the European network on psychosis, affective disorders and cognitive trajectory (ENPACT) study. PLoS One. 2017;12(11):e0188000.
10. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010 Jul;167(7):748–51.
11. Kempton MJ, Geddes JR, Ettinger U, Williams SCR, Grasby PM. Meta-analysis, database, and Meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry. 2008;65:1017.
12. Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and Periventricular Structural Volumes in First- Versus Multiple-Episode Bipolar Disorder. Am J Psychiatry. 2002;159:1841–7.
13. Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI, Frye MA, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatry. 2013;47:321–32.
14. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011;69:326–35.
15. Sagar R, Pattanayak RD. Potential biomarkers for bipolar disorder: where do we stand? Indian J Med Res. 2017;145:7–16.
16. Brambilla P, Hatch JP, Soares JC. Limbic changes identified by imaging in bipolar patients. Curr Psychiatry Rep. 2008;10:505–9.
17. Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ, Pung CJ, et al. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 2010;68:41–50.
18. Fries GR, Bauer IE, Scaini G, Valvassori SS, Walss-Bass C, Soares JC et al. Accelerated hippocampal biological aging in bipolar disorder. Bipolar Disord 2019; : bdi.12876.
19. Selvaraj S, Arnone D, Job D, Stanfield A, Farrow TF, Nugent AC, et al. Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. Bipolar Disord. 2012;14:135–45.
20. Altshuler L, Bartzokis G, Grieder T, Curran J, Mintz J. Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specificity. Arch Gen Psychiatry. 1998;55(7):663–4.
21. Savitz J, Nugent AC, Bogers W, Liu A, Sills R, Luckenbaugh DA, et al. Amygdala volume in depressed patients with bipolar disorder assessed using high resolution 3T MRI: the impact of medication. Neuroimage. 2010;49:2966–76.
22. Wijeratne C, Sachdev S, Wen W, Piguet O, Lipnicki DM, Malhi GS, et al. Hippocampal and amygdala volumes in an older bipolar disorder sample. Int Psychogeriatrics. 2013;25:54–60.
23. van Erp TG, Thompson PM, Kieseppa T, Bearden CE, Marino AC, Hoftman GD, Haukka J, Partonen T, Huttunen M, Kaprio J, La¶nnqvist J, Poutanen VP, Toga AW, Cannon TD. Hippocampal morphology in lithium and non-lithium-treated bipolar I disorder patients, non-bipolar co-twins, and control twins. Hum Brain Mapp 2012;3:501–510.
24. Quigley SJ, Scanlon C, Kilmartin L, Emsell L, Langan C, Hallahan B, et al. Volume and shape analysis of subcortical brain structures and ventricles in euthymic bipolar I disorder. Psychiatry Res. 2015;233:324–30.
25. Lu CF, Wu YT, Teng S, Wang PS, Tu PC, Su TP, et al. Genetic predisposition and disease expression of bipolar disorder reflected in shape changes of the anterior limbic network. Brain Sci. 2019;9(9):240.
26. Sarrazin S, Cachia A, Hozer F, McDonald C, Emsell L, Cannon DM, et al. Neurodevelopmental subtypes of bipolar disorder are related to cortical folding patterns: an international multicenter study. Bipolar Disord. 2018;20(8):721–32.
27. Sun ZY, Houenou J, Duclap D, Sarrazin S, Linke J, Daban C, et al. Shape analysis of the cingulum, uncinate and arcuate fasciculi in patients with bipolar disorder. J Psychiatry Neurosci. 2017;42(1):27–36.
28. Hanford LC, Nazarov A, Hall GB, Sassi RB. Cortical thickness in bipolar disorder: a systematic review. Bipolar Disord. 2016;18:4–18.
29. Brugger SP, Howes OD. Heterogeneity and homogeneity of regional brain structure in schizophrenia: a Meta-analysis. JAMA Psychiatry. 2017;74(11):1104–11.

30. Wannan CMJ, Cropley VL, Chakravarty MM, Bousman C, Ganella EP, Bruggemann JM, et al. Evidence for network-based cortical thickness reductions in schizophrenia. Am J Psychiatry. 2019;176(7):552–63.
31. Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev. 2010;34(4):533–54.
32. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 2002;15:435–55.
33. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics. 2007;4:316–29.
34.• Favre P, Pauling M, Stout J, Hozer F, Sarrazin S, Abé C et al. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals. Neuropsychopharmacology 2019; 44: 2285–2293. **This is a large meta-analysis of structural neuroimaging studies across multiple psychiatric diagnoses.**
35. Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, et al. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. Bipolar Disord. 2004;6:197–203.
36. Beyer JL, Taylor WD, MacFall JR, Kuchibhatla M, Payne ME, Provenzale JM, et al. Cortical white matter microstructural abnormalities in bipolar disorder. Neuropsychopharmacology. 2005;30:2225–9.
37. Haznedar MM, Roversi F, Pallanti S, Baldini-Rossi N, Schnur DB, Licalzi EM, et al. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. Biol Psychiatry. 2005;57:733–42.
38. Sussmann JE, Lymer GKS, Mckirdy J, Moorhead TWJ, Maniega SM, Job D, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disord. 2009;11:11–8.
39. Oertel-Knöchel V, Reinke B, Alves G, Jurcoane A, Wenzler S, Prvulovic D, et al. Frontal white matter alterations are associated with executive cognitive function in euthymic bipolar patients. J Affect Disord. 2014;155:223–33.
40. Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biol Psychiatry. 2011;69(4):309–17.
41. Bellani M, Yeh P-H, Tansella M, Balestrieri M, Soares JC, Brambilla P. DTI studies of corpus callosum in bipolar disorder. Biochem Soc Trans. 2009;37:1096–8.
42. Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. J Affect Disord. 2013;150:192–200.
43. Ji E, Lejuste F, Sarrazin S, Houenou J. From the microscope to the magnet: disconnection in schizophrenia and bipolar disorder. Neurosci Biobehav Rev. 2019;98:47–57.
44. Squarcina L, Bellani M, Rossetti MG, Perlini C, Delvecchio G, Dusi N, et al. Similar white matter changes in schizophrenia and bipolar disorder: a tract-based spatial statistics study. PLoS One. 2017;12.
45. Serafini G, Pompili M, Borgwardt S, Houenou J, Geoffroy PA, Jardri R, et al. Brain changes in early-onset bipolar and unipolar depressive disorders: a systematic review in children and adolescents. Eur Child Adolesc Psychiatry. 2014;23:1023–41.
46. Wei S, Womer FY, Edmiston EK, Zhang R, Jiang X, Wu F, et al. Structural alterations associated with suicide attempts in major depressive disorder and bipolar disorder: a diffusion tensor imaging study. Prog Neuro-Psychopharmacology Biol Psychiatry. 2020;98:109827.
47. Wessa M, Houenou J, Leboyer M, Chanraud S, Poupon C, Martinot JL, et al. Microstructural white matter changes in euthymic bipolar patients: a whole-brain diffusion tensor imaging study. Bipolar Disord. 2009;11:504–14.
48. Bruno S, Cercignani M, Ron MA. White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. Bipolar Disord. 2008;10:460–8.
49. Magioncalda P, Martino M, Conio B, Piaggio N, Teodorescu R, Escelsior A, et al. Patterns of microstructural white matter abnormalities and their impact on cognitive dysfunction in the various phases of type I bipolar disorder. J Affect Disord. 2016;193:39–50.
50.• Pasternak O, Kelly S, Sydnor VJ, Shenton ME. Advances in microstructural diffusion neuroimaging for psychiatric disorders. Neuroimage 2018; 182: 259–282. **This review provides insight on advanced diffusion MRI methods, compares findings across diverse methods, discuss the main benefits and limitations of the different methods.**
51. Tuozzo C, Lyall AE, Pasternak O, James ACD, Crow TJ, Kubicki M. Patients with chronic bipolar disorder exhibit widespread increases in extracellular free water. Bipolar Disord. 2018;20:523–30.
52. Nazeri A, Mulsant BH, Rajji TK, Levesque ML, Pipitone J, Stefanik L, et al. Gray matter Neuritic microstructure deficits in schizophrenia and bipolar disorder. Biol Psychiatry. 2017;82:726–36.
53. Sarrazin S, Poupon C, Teillac A, Mangin JF, Polosan M, Favre P, et al. Higher in vivo cortical intracellular volume fraction associated with Lithium therapy in bipolar disorder: a multicenter NODDI study. Psychother Psychosom. 2019;88(3):171–6.
54. Sarrazin S, Poupon C, Linke J, Wessa M, Phillips M, Delavest M, et al. A multicenter Tractography study of deep white matter tracts in bipolar I disorder. JAMA Psychiatry. 2014;71:388.
55. Canales-Rodríguez EJ, Pomarol-Clotet E, Radua J, Sarró S, Alonso-Lana S, Del Mar BC, et al. Structural abnormalities in bipolar Euthymia: a multicontrast molecular diffusion imaging study. Biol Psychiatry. 2014;76:239–48.
56. Scholz V, Houenou J, Kollmann B, Duclap D, Poupon C, Wessa M. Dysfunctional decision-making related to white matter alterations in bipolar I disorder. J Affect Disord. 2016;194:72–9.
57. Ji E, Guevara P, Guevara M, Grigis A, Labra N, Sarrazin S, et al. Increased and decreased superficial white matter structural connectivity in schizophrenia and bipolar disorder. Schizophr Bull. 2019;45(6):1367–78.
58. Favre P, Houenou J, Baciu M, Pichat C, Poupon C, Bougerol T, et al. White matter plasticity induced by Psychoeducation in bipolar patients: a controlled diffusion tensor imaging study. Psychother Psychosom. 2016;85:58–60.
59. Zhao L, Wang Y, Jia Y, Zhong S, Sun Y, Zhou Z, et al. Cerebellar microstructural abnormalities in bipolar depression and unipolar depression: a diffusion kurtosis and perfusion imaging study. J Affect Disord. 2016;195:21–31.
60. Ota M, Noda T, Sato N, Hidese S, Teraishi T, Setoyama S, et al. The use of diffusional kurtosis imaging and neurite orientation dispersion and density imaging of the brain in bipolar disorder. J Affect Disord. 2019;251:231–4.
61. Angst J. Bipolar disorders in DSM-5: strengths, problems and perspectives. Int J Bipolar Disord. 2013;1(1):12.
62. van Bergen AH, Verkooijen S, Vreeker A, Abramovic L, Hillegers MH, Spijker AT, et al. The characteristics of psychotic features in bipolar disorder. Psychol Med. 2019;49(12):2036–48.
63. Mazzarini L, Colom F, Pacchiarotti I, Nivoli AM, Murru A, Bonnin CM, et al. Psychotic versus non-psychotic bipolar II disorder. J Affect Disord. 2010;126(1–2):55–60.
64. Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, et al. The neurocognitive signature of psychotic bipolar disorder. Biol Psychiatry. 2007;62(8):910–6.
65. Dell'Osso B, Camuri G, Cremaschi L, Dobrea C, Buoli M, Ketter TA, et al. Lifetime presence of psychotic symptoms in bipolar

disorder is associated with less favorable socio-demographic and certain clinical features. Compr Psychiatry. 2017;76:169–76.
66. Bonnin CM, Jimenez E, Sole B, Torrent C, Radua J, Reinares M, et al. Lifetime psychotic symptoms. Subthreshold Depression and Cognitive Impairment as Barriers to Functional Recovery in Patients with Bipolar Disorde J Clin Med. 2019;8.
67. Tohen M, Hennen J, Zarate CM Jr, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry. 2000;157(2):220–8.
68. Reininghaus U, Bohnke JR, Hosang G, Farmer A, Burns T, McGuffin P, et al. Evaluation of the validity and utility of a transdiagnostic psychosis dimension encompassing schizophrenia and bipolar disorder. Br J Psychiatry. 2016;209(2):107–13.
69. Ruderfer DM, Ripke S, McQuillin A, Boocock J, Stahl EA, Pavlides JMW, et al. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell. 2018;173(7): 1705–15.
70. Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M, et al. A test of the Transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. JAMA Psychiatry. 2017;74(12):1206–13.
71. Yatham LN, Liddle PF, Shiah IS, Lam RW, Ngan E, Scarrow G, et al. PET study of [(18)F]6-fluoro-L-dopa uptake in neuroleptic- and mood-stabilizer-naive first-episode nonpsychotic mania: effects of treatment with divalproex sodium. Am J Psychiatry. 2002;159(5):768–74.
72. Ivleva EI, Clementz BA, Dutcher AM, Arnold SJM, Jeon-Slaughter H, Aslan S, et al. Brain structure biomarkers in the psychosis biotypes: findings from the bipolar-schizophrenia network for intermediate phenotypes. Biol Psychiatry. 2017;82(1): 26–39.
73. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 2010;117(1):1–12.
74. Yu K, Cheung C, Leung M, Li Q, Chua S, McAlonan G. Are bipolar disorder and schizophrenia Neuroanatomically distinct? An Anatomical Likelihood Meta-analysis Front Hum Neurosci. 2010;4:189.
75. Maggioni E, Altamura AC, Brambilla P. Exploring the neuroanatomical bases of psychotic features in bipolar disorder. Epidemiol Psychiatr Sci. 2017;26(4):358–63.
76. Wang X, Tian F, Wang S, Cheng B, Qiu L, He M, et al. Gray matter bases of psychotic features in adult bipolar disorder: a systematic review and voxel-based meta-analysis of neuroimaging studies. Hum Brain Mapp. 2018;39(12):4707–23.
77. Chen X, Wen W, Malhi GS, Ivanovski B, Sachdev PS. Regional gray matter changes in bipolar disorder: a voxel-based morphometric study. Aust N Z J Psychiatry. 2007;41(4):327–36.
78. Keramatian K, Dhanoa T, McGirr A, Lang DJ, Honer WG, Lam RW, et al. Structural brain changes in first episode mania with and without psychosis: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). World J Biol Psychiatry 2018;19(sup2):S30-S40.
79. Laidi C, d'Albis MA, Wessa M, Linke J, Phillips ML, Delavest M, et al. Cerebellar volume in schizophrenia and bipolar I disorder with and without psychotic features. Acta Psychiatr Scand. 2015;131(3):223–33.
80. Mamah D, Alpert KI, Barch DM, Csernansky JG, Wang L. Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. Neuroimage Clin. 2016;11:276–86.
81. Neves Mde C, Duarte DG, Albuquerque MR, Nicolato R, Neves FS, Souza-Duran FL, et al. Neural correlates of hallucinations in bipolar disorder. Braz J Psychiatry. 2016;38(1):1–5.
82. Radaelli D, Poletti S, Gorni I, Locatelli C, Smeraldi E, Colombo C, et al. Neural correlates of delusion in bipolar depression. Psychiatry Res. 2014;221(1):1–5.
83. Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, Pulver AE, et al. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. Biol Psychiatry. 2005;57(6):633–9.
84. Womer FY, Wang L, Alpert KI, Smith MJ, Csernansky JG, Barch DM, et al. Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder. Psychiatry Res. 2014;223(2):75–83.
85. Altamura AC, Maggioni E, Dhanoa T, Ciappolino V, Paoli RA, Cremaschi L, et al. The impact of psychosis on brain anatomy in bipolar disorder: a structural MRI study. J Affect Disord. 2018;233:100–9.
86. Ekman CJ, Petrovic P, Johansson AG, Sellgren C, Ingvar M, Landen M. A history of psychosis in bipolar disorder is associated with gray matter volume reduction. Schizophr Bull. 2017;43(1): 99–107.
87. Squarcina L, Perlini C, Peruzzo D, Castellani U, Marinelli V, Bellani M, et al. The use of dynamic susceptibility contrast (DSC) MRI to automatically classify patients with first episode psychosis. Schizophr Res. 2015;165(1):38–44.
88. Squarcina L, De Luca A, Bellani M, Brambilla P, Turkheimer FE, Bertoldo A. Fractal analysis of MRI data for the characterization of patients with schizophrenia and bipolar disorder. Phys Med Biol. 2015;60(4):1697–716.
89. Fries GR, Pfaffenseller B, Stertz L, Paz AVC, Dargél AA, Kunz M, et al. Staging and neuroprogression in bipolar disorder. Current Psychiatry Reports. 2012;14(6):667–75.
90. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134: 2456–77.
91. Kendler KS. The clinical features of mania and their representation in modern diagnostic criteria.Psychol Med 2017;47(6):1013–1029.
92. Gildengers AG, Mulsant BH, Begley A, Mazumdar S, Hyams AV, Reynolds Iii CF, et al. The longitudinal course of cognition in older adults with bipolar disorder. Bipolar Disord. 2009;11:744–52.
93. Schouws SN, Stek ML, Comijs HC, Dols A, Beekman AT. Cognitive decline in elderly bipolar disorder patients: a follow-up study. Bipolar Disord. 2012;14(7):749–55.
94. Delaloye C, Moy G, de Bilbao F, Weber K, Baudois S, Haller S, et al. Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. Int J Geriatr Psychiatry. 2011;26(12):1309–18.
95. Depp CA, Savla GN, Moore DJ, et al. Short-term course of neuropsychological abilities in middle-aged and older adults with bipolar disorder. Bipolar Disord. 2008;10(6):684–90.
96. Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord. 2003;73:261–9.
97. Kessing LV, Hansen MG, Andersen PK, Angst J. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders – a life-long perspective. Acta Psychiatr Scand. 2004;109:339–44.
98. da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry. 2013;202(3):177–86.
99. Galimberti D, Fenoglio C, Serpente M, Villa C, Bonsi R, Arighi A, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: late-onset psychotic clinical presentation. Biol Psychiatry. 2013;74(5):384–91.

100. Devenney EM, Ahmed RM, Halliday G, Piguet O, Kiernan MC, Hodges JR. Psychiatric disorders in C9orf72 kindreds: study of 1, 414 family members. Neurology. 2018;91(16):e1498–507.
101. Galimberti D, Reif A, Dell'Osso B, Palazzo C, Villa C, Fenoglio C, et al. C9ORF72 hexanucleotide repeat expansion as a rare cause of bipolar disorder. Bipolar Disord. 2014;16(4):448–9.
102. Cheran G, Silverman H, Manoochehri M, Goldman J, Lee S, Wu L, et al. Psychiatric symptoms in preclinical behavioural-variant frontotemporal dementia in MAPT mutation carriers. J Neurol Neurosurg Psychiatry. 2018;89(5):449–55.
103. Rubino E, Vacca A, Gallone S, Govone F, Zucca M, Gai A, et al. Late onset bipolar disorder and frontotemporal dementia with mutation in progranulin gene: a case report. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(7–8):624–6.
104. Vijverberg EG, Wattjes MP, Dols A, Krudop WA, Möller C, Peters A, et al. Diagnostic accuracy of MRI and additional [18F]FDG-PET for behavioral variant Frontotemporal dementia in patients with late onset behavioral changes. J Alzheimers Dis. 2016;53(4): 1287–97.
105. Vijverberg EGB, Gossink F, Krudop W, Sikkes S, Kerssens C, Prins N, et al. The diagnostic challenge of the late-onset frontal lobe syndrome: clinical predictors for primary psychiatric disorders versus behavioral variant Frontotemporal dementia. J Clin Psychiatry. 2017;78(9):e1197–203.
106. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. Mol Psychiatry. 2017;22(10):1455–63.
107. Haldane M, Frangou S. New insights help define the pathophysiology of bipolar affective disorder: neuroimaging and neuropathology findings. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28(6):943–60.
108. Schroeter ML, Laird AR, Chwiesko C, Deuschl C, Schneider E, Bzdok D, et al. Conceptualizing neuropsychiatric diseases with multimodal data-driven meta-analyses - the case of behavioral variant frontotemporal dementia. Cortex. 2014;57:22–37.
109. Rosen HJ, Gorno-Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology. 2002;58:198–208.
110. Whitwell JL, Przybelski SA, Weigand SD, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. Brain. 2009;132(pt 11):2932–46.
111. Borroni B, Brambati SM, Agosti C, Gipponi S, Bellelli G, Gasparotti R, et al. Evidence of white matter changes on diffusion tensor imaging in frontotemporal dementia. Arch Neurol. 2007;64(2):246–51.
112. Matsuo K, Mizuno T, Yamada K, Akazawa K, Kasai T, Kondo M, et al. Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. Neuroradiology. 2008;50(7):605–11.
113. Agosta F, Scola E, Canu E, Marcone A, Magnani G, Sarro L, et al. White matter damage in frontotemporal lobar degeneration spectrum. Cereb Cortex. 2012;22(12):2705–14.
114. Dong D, Wang Y, Chang X, Jiang Y, Klugah-Brown B, Luo C, et al. Shared abnormality of white matter integrity in schizophrenia and bipolar disorder: a comparative voxel-based meta-analysis. Schizophr Res. 2017;185:41–50.
115. Ganzola R, Duchesne S. Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls. Bipolar Disord. 2017 Mar;19(2):74–83.
116. Baez S, Pinasco C, Roca M, Ferrari J, Couto B, García-Cordero I, et al. Brain structural correlates of executive and social cognition profiles in behavioral variant frontotemporal dementia and elderly bipolar disorder. Neuropsychologia. 2019;126:159–69.
117. Delvecchio G, Mandolini GM, Arighi A, Prunas C, Mauri CM, Pietroboni AM, et al. Structural and metabolic cerebral alterations between elderly bipolar disorder and behavioural variant frontotemporal dementia: a combined MRI-PET study. Aust N Z J Psychiatry. 2019;53(5):413–23.
118. Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. Br J Psychiatry. 2009;195(3):194–201.
119. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011;69(4):326–35.