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Review article

A ventral prefrontal-amygdala neural system in bipolar disorder: a view from neuroimaging research

Womer FY, Kalmar JH, Wang F, Blumberg HP. A ventral prefrontal-amygdala neural system in bipolar disorder: a view from neuroimaging research.

In the past decade, neuroimaging research has identified key components in the neural system that underlies bipolar disorder (BD). The ventral prefrontal cortex (VPFC) and amygdala are highly interconnected structures that jointly play a central role in emotional regulation. Numerous research groups have reported prominent structural and functional abnormalities within the VPFC and amygdala supporting their essential role in a neural system underlying the emotional dysregulation that is a core feature of BD. Findings in BD also include those in brain regions interconnected with the VPFC and amygdala, including the ventral striatum, hippocampus and the cerebellum. Abnormalities in these regions may contribute to symptoms that reflect disruption in functions sub-served by these structures, including motivational, mnemonic and psychomotor functions.

This article will first review leads from behavioural neurology that implicated these neural system abnormalities in BD. It will then review findings from structural and functional imaging studies to support the presence of abnormalities *within* these neural system components in BD. It will also review new findings from studies using diffusion tensor imaging (DTI) that provide increasing evidence of abnormalities in the connections *between* these neural system components in BD. Emerging data supporting differences in this neural system during adolescence, as well as potential beneficial effects of treatment on structure and function will also be presented. Finally, the article will discuss the implications for future investigations, including those for early identification and treatment of BD.

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Introduction

Bipolar disorder (BD) manifests as cycling between the acute emotional elevations of manic episodes and the acute dysphoria of depressive episodes. The sustained affective states of these episodes are accompanied by disruptions in a broad range of associated behaviours. These include disturbances in neurovegetative functions such as sleep, appetite and sexual drives, excesses or constriction in motivated behaviour, thought abnormalities that are often coloured by the affective state and can reach the level of psychosis, and disruptions in cognitive functions. A brain model for BD would ideally account for these characteristic emotional, neurovegetative, behavioural and cognitive abnormalities in the disorder, as well as its cyclic nature. Additionally, such a model would also account for abnormalities observed during periods between episodes. Although BD has long been thought of as an illness with return to excellent premorbid level of functioning between episodes, it is evident that many individuals with BD do not follow such a course and may experience protracted symptoms and disability even during euthymic periods (1–5).

Over the past decade, substantial effort has been put forth in neuroimaging research to understand the neural system abnormalities underlying BD. Significant progress has been made in identifying regional

brain differences that likely contribute to the symptoms of acute episodes of BD. In the following text, evidence will be presented to support prominent abnormalities in a ventral prefrontal cortex (VPFC)-amygdala neural system thought to play a key role in the emotional dysregulation of BD and that through its connections with structures such as the ventral striatum, hippocampus, cerebellum and hypothalamus could also contribute to the range of associated symptoms. Moreover, in recent years, subtle differences in this neural system, especially in the VPFC, have been identified during euthymic periods. This suggests trait disturbances that may confer susceptibility to features such as cycling that if characterized, could be targeted in preventive treatment efforts designed to bolster the resiliency of this neural system.

Leads from behavioural neurology

Behavioural neurology provided an initial guide to localise key brain regions involved in BD. Since at least the 1800s, affective and behavioural changes similar to those observed in BD have been reported in individuals with lesions in the VPFC (6–11). [Please note that in this article the VPFC will be defined broadly to include orbitofrontal cortex (OFC), inferior and rostral frontal cortices, and the ventral and pregenual components of the anterior cingulate cortex (ACC).] In particular, these changes consist of difficulties in adaptively regulating motivational drives for engaging in pleasurable and risky behaviours despite awareness of the associated negative consequences, as can occur during manic episodes of BD (6,8,11). Furthermore, lesion studies have suggested that the valence of the mood symptomatology depends on the hemispheric lateralisation of the lesion. Individuals with left hemisphere frontal lesions appear more likely to become depressed whereas those with right hemisphere lesions more often experience mania (12–14).

Studies of behaviours associated with seizures have also implicated brain regions involved in BD, particularly regions that probably exhibit excessive activity in the disorder. Flor Henry described BD-type symptoms in patients who had complex partial seizures with mesial temporal seizure foci encompassing the amygdala (15). Bear and Fedio also observed BD-type symptoms associated with complex partial seizures of temporal lobe origin and additionally, they noted hemispheric lateralisation with respect to the emotional valence of behavioural changes (16). Paranoia and diminished humour, characteristic of depressive episodes, were associated with left-sided foci whereas elation, emotionality and hypersexuality, characteristic of manic episodes, were associated with right-sided foci.

Behavioural neurology highlighted the VPFC and amygdala as two key components in affect regulation as well as underscored the importance of hemispheric lateralisation in the valence of emotional behaviour. It suggested a model in which deficits in VPFC functioning and excesses in amygdala activity could produce BD-type symptoms. Given the significant reciprocal inhibitory connections between the VPFC and amygdala and the important role of the top-down VPFC regulation of amygdala responses in emotional behaviour through these connections (17), it suggested that disruptions in VPFC top-down regulation of the system could lead to the loss of affective homeostasis in BD. However, excesses in amygdala activity themselves could also contribute to the extremes in emotional behaviours seen in BD.

Literature from behavioural neurology has also suggested that disruptions in the white matter connections within this VPFC-amygdala neural system could contribute to the BD phenotype as well. Altered emotional and motivational states associated with lesions involving both intra-hemispheric fronto-subcortical connections and inter-hemispheric connections through the corpus callosum (CC) have been observed as early as the beginning of the 20th century by Starr (18). In support of these reports, genetic and postmortem studies have found glial cell, specifically oligodendrocyte, and myelination abnormalities in BD (19–26), leading to a recent surge in studies of white matter integrity and functional connectivity in BD.

In light of a postulated VPFC-amygdala neural system in BD, connections of the VPFC and amygdala point to other brain regions that may sub-serve additional functions disrupted in BD. These regions include the mesial temporal hippocampus, subcortical structures such as the ventral striatum and thalamus, the cerebellum and the hypothalamus (27–33). Associated disruptions in the functioning of these structures could account for the range of symptoms observed in BD. For example, the hippocampus plays an important role in memory and therefore is implicated in the cognitive deficits observed in individuals with BD (34–38). Given the role of the ventral striatum in motivation and reward behaviours, ventral striatal abnormalities could contribute to the hedonic excesses of mania and anhedonia of depression (39). The cerebellum plays key roles in motor function and may influence the psychomotor disturbances of depression and mania. Additionally its known involvement in behavioural timing suggests that the cerebellum may influence emotional rhythmicity and timing and potentially mood

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cycling (40–42). The hypothalamus is important in the regulation of circadian rhythms including sleep, as well as appetite and sexual behaviours, implicating its influence in the neurovegetative symptoms of BD. Evidence of the involvement of these regions in BD from neuroimaging research are emerging as will be reviewed. Unfortunately, study of the hypothalamus in BD has been limited by the constraints of current imaging methods.

Behavioural neurology has provided important leads in the efforts to understand the neural system contributing to BD. Over the past decade, neuroimaging research has expanded upon these leads. It has identified the VPFC and amygdala as central components in the neural system underlying BD and the other connected brain regions as important contributors to the disruptions of this system. This article will review the findings from structural and functional imaging to support this neural system model of BD. First, the presence of abnormalities within the neural components involved in BD will be discussed, particularly in the VPFC and amygdala, as well as in the hippocampus, striatum, thalamus and cerebellum. Then, diffusion tensor imaging (DTI) findings of abnormalities in the connections between the neural system components in BD will be reviewed. Finally, implications for future studies and for early identification and treatment of BD will be discussed.

Structural neuroimaging studies of BD

VPFC

In 1997, Drevets et al. provided a seminal report showing reduced grey matter volume in left subgenual prefrontal cortex in adults with BD (43). Since that time, numerous groups have reported decreased volumes of frontal sub-regions in adults with BD (44–50). This has been striking as different research groups have utilised various methods for analysing neuroimaging data (43–56). This view is supported by consistent findings in post-mortem studies of decreased cellular density in the VPFC in BD (21,22). A potential role for the VPFC in vulnerability to mood cycling is suggested by a reported association between greater magnitude of VPFC volume decreases in BD and rapid cycling (44). However, it is also possible that VPFC volume decreases are a result of recurrent affective episodes. Further studies that clarify the role of specific sub-regions within the VPFC in BD, and their associations to cycling, will be important for understanding the role of the VPFC in the disorder. Additionally, future studies in the VPFC will also need to consider individual differences in its anatomy. For example, Fornito et al. point out that anatomy can vary across individuals, such as in the appearance of specific sulcal and gyral morphological patterns, which often has not been accounted for in morphological studies (46).

Among studies of the VPFC in adolescents with BD, there are some disparate findings, including reports of no differences in the VPFC (52–58). The variability in findings could be related to developmental influences on the VPFC. In both an earlier cross-sectional study and a more recent longitudinal within-subject study, Blumberg et al. and Kalmar et al. have noted age-related decline in VPFC volumes that appear accelerated in adolescents and young adults with BD, implicating differences in VPFC neurodevelopment in BD (44,53,59). This suggests an interaction between the maturation of the VPFC during adolescence and the disorder, and possible abnormalities in the mechanisms that underlie structural maturation of the VPFC during this epoch in BD (59). The potential progression of the VPFC differences over adolescence could affect the detection of VPFC differences in BD samples depending on the maturational stage of the study participants (56).

Effects of medication on VPFC volumes have been reported as well. Pre-clinical studies provide compelling evidence for neurotrophic and neuroprotective effects of mood-stabilising medications that are used to treat BD, including lithium and valproate, on cortico-limbic structures (60). In 2000, Moore et al. reported cortical grey matter increases in individuals with BD following 4 weeks of lithium treatment (61). Since that report, several cross-sectional studies found larger frontal volumes in individuals with BD treated with mood-stabilising medications as compared with individuals with the disorder who were unmedicated at the time of study (44,62,63). A recent longitudinal within-subject study of healthy individuals found increases in prefrontal volume after 4 weeks of lithium treatment (64). In addition, increases in cortical grey matter have been reported in BD individuals treated with lithium (65).

Amygdala

While some studies have reported amygdala volume decreases in adults with BD, others have reported increases or no differences in volume among BD adults (66–69). The discrepant findings could relate to salient differences between clinical subtypes within BD, such as early-onset BD and BD with psychotic features, as well as differences in demographic characteristics, such as age and sex, developmental factors, duration of illness and medication exposure (67). Evidence also indicates potential effects of

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genetic polymorphisms on amygdala volume, such as the 5-hydroxytryptamine transporter-linked polymorphic region (5-HTTLPR) genotype (70).

In contrast to the studies of BD adults, studies of BD adolescents have reported highly consistent findings of amygdala volume decreases (57,67,71–73). The differences in findings between adults and adolescents with BD may relate to fewer recurrences of affective episodes or shorter duration of illness in adolescents than in adults. They may also reflect less exposure to medications in adolescents compared with adults. Amygdala volumes have been reported to be larger in both adolescents and adults who were taking mood-stabilising medication at the time of study as compared with those who were not, suggesting possible neurotrophic effects of these medications in the amygdala (71,74). Alternatively, the differences may also indicate that early-onset BD represents a separable phenotype within BDs.

Associated structures

The hippocampus has had variable findings of volume abnormalities with reports of significant or trend-level decreases or no differences in BD adolescents (67,71,75,76) and adults (66–69,77–82). Multiple factors could contribute to the variable findings including differences related to sex (76) and increases in volume in association with mood stabilisers (75) as well as contribution from genetic variation (83,84). The hippocampus is one of the first structures in which volume differences were associated with a specific genetic variation in BD. Chepenik et al. reported smaller hippocampus volumes with decreases most prominent in the left hippocampus in BD individuals carrying the brain-derived neurotrophic growth factor (*BDNF*) *Val66Met* allele, compared with healthy individuals and BD individuals not carrying the *met* allele (83). A longitudinal study of adults with BD also showed an association between the BDNF *Val66Met* polymorphism and temporal grey matter loss that included the left hippocampus (84). These findings suggest genetic subtypes within BD that have particular vulnerability for volume deficits in the hippocampus.

Alterations in the other previously discussed brain regions implicated in BD have also been observed. Decreases in volume localised to the nucleus accumbens have been found (57). Studies have reported differences in basal ganglia volume or shape especially in individuals with BD who were unmedicated (73,85,86). Abnormalities in the cerebellar vermis associated with the number of prior affective episodes (87–89) and family history of BD (90) have been reported as well.

Functional neuroimaging studies of BD

VPFC

As functional neuroimaging studies capture regional brain activity that reflects the mental state at the time of scanning, such studies that have been performed during manic, depressed and euthymic states of BD have revealed both mood state- and trait-dependent features of the disorder. As predicted by the lesion studies described previously, mania has primarily been associated with deficits in VPFC activation that tends to be more lateralised to the right hemisphere across a variety of emotion and cognitive processing tasks (91–95). Depressive states in BD have been more associated with relative increases in VPFC activation that tends to be left-lateralized (92,96,97). Increasingly studies across mood states in BD, and specifically of euthymic individuals, show VPFC abnormalities that suggest differences in VPFC functioning may be associated with the BD trait in adults (92,98–102).

As noted with VPFC structural abnormalities, VPFC functional abnormalities may also progress over adolescence and young adulthood. In a preliminary cross-sectional study, Blumberg et al. noted that VPFC activation increased with age in healthy adolescents who were performing a colour-naming Stroop task, consistent with the view that the VPFC increasingly comes online with age in the service of providing adaptive inhibition of prepotent response tendencies (103). This age-related pattern was not seen in adolescents with BD suggesting an alteration in this functional maturation of the VPFC in BD. In other studies of adolescents, VPFC deficits have been noted during commission errors on a stop-signal task (104) as well as both increases and decreases in VPFC activation relative to controls during the performance of emotional processing tasks (105,106). These studies suggest that some aspects of BD-related VPFC functional abnormalities may emerge during adolescence and may progress during this epoch in BD.

Mood-stabilizing pharmacotherapy has been associated with reduction of differences in VPFC activation. Deficits in activation were diminished in individuals taking mood-stabilizing medications as compared with those who were not taking medication at the time of scanning (98,107). The mechanisms underlying the reversal of functional deficits are not known; their elucidation could prove important for developing new treatment strategies for BD. One possibility is raised by a recent study of the 5-HTTLPR polymorphism in BD showing effects on regional brain function in the disorder that were most prominent in the ventral ACC, which has a high concentration of serotonin receptors (108). This suggests

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that mechanisms related to serotonergic transmission may have influences especially in the ventral ACC region in BD and individuals may respond to serotonergic interventions differently depending on their genetic composition.

Amygdala

Functional neuroimaging studies of individuals with BD at rest or performing emotional processing tasks during scanning have been relatively consistent in observing abnormal elevations in amygdala activation (97,98,105–107,109–115). These findings have been reported in both adolescents and adults with BD, irrespective of mood state. This suggests that dysregulated amygdala activity may be an early trait feature of BD.

As observed in the VPFC, mood-stabilizing pharmacotherapy has also been associated with reduction of differences in activation in the amygdala. Excess activation in the amygdala appears to be blunted by mood-stabilizing medication (98,107,111). As in the VPFC, the mechanisms contributing to the reversal of functional differences in the amygdala are unclear. The reversal may reflect theorised mood-stabilising effects achieved through restoration of homeostatic balance of excitatory glutamate as compared to inhibitory gamma amino butyric acid (GABA) activity (116). This potential mechanism is supported by studies of anti-convulsant effects on synaptic neurotransmission in the amygdala. For example, lamotrigine has shown effects on GABA transmission in the amygdala (117), and valproic acid has been suggested to influence excitatory synaptic responses mediated by NMDA receptors in the amygdala (118).

Associated structures

Activation differences in other subcortical structures have also been reported in BD. The thalamus and striatum have shown functional abnormalities during both acute episodes and euthymic periods in BD adolescents (103,110) and adults (97,112,119–121). These abnormalities may also be reversed by medication (120,122).

Functional neuroimaging studies have also noted abnormalities in the cerebellum among euthymic adults with BD (112,123,124). Decreased activation in the cerebellum has been observed in response to positive affect induction and during a counting Stroop interference task (123,124). Additionally, abnormalities in cerebellar blood flow in BD have also been shown (112). These abnormalities may be influenced by antipsychotic treatment (125).

White matter integrity and connectivity

Decreases in glial cells, particularly oligodendrocytes, in both frontal regions and the amygdala, as well as down-regulation of oligodendrocyte- and myelin-related genes in frontal regions in BD, suggest the presence of white matter abnormalities in the disorder (19–25). Moreover, findings of alteration in grey matter brain regions that are highly interconnected further support the presence of abnormalities within the white matter that connect these structures. Structural magnetic resonance imaging (MRI) studies have shown decreases in frontal white matter volume in adults with BD (44,50,126–128). In addition, abnormalities within the CC such as decreased midsagittal CC areas have been reported in adults with BD (126,127,129–131). This is of particular interest as the anterior component of the CC provides interhemispheric connections between the left and right prefrontal cortices thought to integrate hemispheric functioning and to play a key role in the integration of emotional and cognitive information (132).

To further characterise the findings of white matter abnormalities observed by structural imaging, DTI methods have recently been implemented in the study of BD. These methods may be more sensitive to detecting microstructural differences within white matter connections of regions involved in BD than structural MRI morphometry methods. Fractional anisotropy (FA) is one of the principal DTI measures that has been utilised and that provides an index of the coordinated directionality of fibres within white matter fibre bundles (133). DTI studies of BD have shown differences in FA primarily in ventral frontal regions, in regions carrying fibers between the VPFC and the amygdala, hippocampus, striatum and thalamus as well as in the CC (134–142). As research efforts utilising DTI progress, methods to isolate and intensively study specific white matter bundles of interest are emerging, especially those key in the neural circuitry of BD. For example, Wang et al. used methods to define the anterior region of the cingulum bundle (142). This cingulum sub-region is especially implicated in BD as it provides substantial connections between the regions discussed above. Wang et al. showed decreases in FA in the anterior cingulum in adults with BD, as compared with a healthy group of adults (142). Another bundle of particular interest in BD is the uncinate fasciculus, a ventral white matter structure that inter-connects the VPFC and amygdala. Utilising tract-based spatial statistics, Versace et al. found abnormalities in FA in the uncinate fasciculus in adults with BD (140). The above findings support abnormalities in the ventral white matter that provides significant connectivity within the VPFC-amygdala neural system in BD.

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Conclusions and future directions for the field of BD neuroimaging research

Studies examining changes in behaviour associated with lesions and seizures laid important groundwork for identifying the brain regions involved in BD. Since those studies, the field of BD research has advanced in understanding the structural and functional disruptions within the neural system contributing to BD and has progressed in the neuroimaging techniques used to study these disruptions. Recent developments in the field include studies that integrate multiple neuroimaging modalities to examine the relationships between grey and white matter and between structure and function. For example, a recent study in the amygdala combined structural and functional magnetic resonance imaging (fMRI) methods to show a significant inverse association between volume decreases and activation increases in adolescents with BD suggesting a mechanistic relationship between the structural and functional abnormalities observed (143). Another study integrated fMRI functional connectivity and DTI methods to show associations between abnormalities in VPFC-amygdala coordinated activity and the structural integrity of the white matter that connects them suggesting that white matter abnormalities may contribute to functional disruptions in the brain circuitry of BD (144).

As neuroimaging research advances, a comprehensive neural system model for BD is evolving. Evidence suggests that the VPFC, the amygdala, and their interactions are critical and central to the neuropathophysiology of the disorder. Data support influences by other brain structures interconnected with the VPFC and amygdala, such as the hippocampus, ventral striatum, thalamus and cerebellum, on the neural system contributing to BD. The specific mechanisms of such influences are unclear. However, these structures may mutually affect one another's development and function. Additionally, findings indicate effects of genetic, developmental and treatment factors on this VPFC-amygdala neural system as well. In this VPFC-amygdala neural system model of BD, a complex interplay of different influences leads to disruptions within the neural circuitry that manifest in the range of BD symptoms, including affective episodes, mood cycling, cognitive disturbances, neurovegetative symptoms and psychomotor disturbances. Although the proposed model highlights the central role of the VPFC and amygdala in BD, the potential contribution by other brain regions to the disorder is also important. Thus, efforts to understand such contributions should continue in conjunction with those to elucidate the roles of the VPFC and amygdala in BD. Such investigations may lead to mapping of specific BD symptoms, such as mood cycling or cognitive disturbances, onto certain components of the neural system underlying the disorder.

As a neural system model of BD emerges, there is a great hope for the application of research findings to the timely and accurate diagnosis and effective treatment of BD. Work to translate findings from neuroimaging research to prevention and treatment strategies for BD has commenced. Findings of structural and functional brain abnormalities in adolescents with BD suggest that alterations in the development and function of some brain regions may emerge in adolescence and may progress during this epoch when the symptoms of BD often first present (59). In conjunction with reports that suggest the beneficial effects of medication on structural and functional abnormalities in BD, these findings emphasise the importance of early identification and treatment strategies. The differentiation of BD from other psychiatric disorders such as attention-deficit hyperactivity disorder and major depressive disorder among adolescents and young adults remains challenging. With the progress in the BD imaging field, future investigations can focus on direct comparisons between these disorders in adolescents and young adults. Such comparison studies could contribute significantly to improving diagnosis of BD in adolescents and young adults. Furthermore, studies of youths with BD, as well as emerging studies of unaffected family members at-risk for BD, could prove pivotal for the development of tools to identify and intervene early in those vulnerable to BD. Additionally, the emergence of studies that show influence of specific genetic variations on the brain circuitry of BD hold particular promise as they can point to specific molecular mechanisms that could be targeted for the development of new preventive and treatment strategies.

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References

1. Judd LL, Akiskal HS, Schettler PJ et al. Psychosocial disability in the course of bipolar I and II disorders:a

https://doi.org/10.1111/j.1601-5215.2009.00414.x Published online by Cambridge University Press

prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;**62**:1322–1330.
2. Goldstein TR, Birmaher B, Axelson D et al. Psychosocial functioning among bipolar youth. J Affect Disord 2009;**114**:174–183.
3. Huxley N, Baldessarini RJ. Disability and its treatment in Bipolar disorder patients. Bipolar Disord 2007;**9**: 183–196.
4. Marangell LB, Dennehy EB, Miyahara S, Wisniewski SR, Bauer MS, Rapaport MH, Allen MH. The functional impact of subsyndromal depressive symptoms in bipolar disorder:Data from STEP-BD. J Affect Disord 2008;**114**:58–67.
5. Sajatovic M. Bipolar disorder: disease burden. Am J Manag Care 2005;**11**:S80–S84.
6. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 1999;**19**:5473–5481.
7. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. Am J Psychiatry 1984;**141**: 1084–1087.
8. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science 1994;**264**:1102–1105.
9. Jastrowitz M. Beitrage zur localisation im grosshirn and uber deren praktische verwerthung. Dtsch Med Wochenshr 1888;**14**:81–83.
10. Oppenheim H. Zur pathologie der grosshirngeschwulste. Arch Psychiatry 1889;**21**:560–578.
11. Rolls ET, Hornak J, Wade D, Mcgrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry 1994;**57**:1518–1524.
12. Sackeim HA, Greenberg MS, Weiman AL, Gur RC, Hungerbuhler JP, Geschwind N. Hemispheric asymmetry in the expression of positive and negative emotions. Neurologic evidence. Arch Neurol 1982;**39**:210–218.
13. Starkstein SE, Bryer JB, Berthier ML, Cohen B, Price TR, Robinson RG. Depression after stroke: the importance of cerebral hemisphere asymmetries. J Neuropsychiatry Clin Neurosci 1991;**3**:276–285.
14. Wexler BE. Cerebral laterality and psychiatry: a review of the literature. Am J Psychiatry 1980;**137**:279–291.
15. Flor-Henry P. Schizophrenic-like reactions and affective psychoses associated with temporal lobe epilepsy: etiological factors. Am J Psychiatry 1969;**126**:400–404.
16. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. Arch Neurol 1977;**34**:454–467.
17. Rolls ET. The functions of the orbitofrontal cortex. Brain Cogn 2004;**55**:11–29.
18. Starr MA. Organic nervous diseases. New York: Lea Brothers & Co., 1903.
19. Bowley MP, Drevets WC, Ongur D, Price JL. Low glial numbers in the amygdala in major depressive disorder. Biol Psychiatry 2002;**52**:404–412.
20. Kim S, Webster MJ. Correlation analysis between genome-wide expression profiles and cytoarchitectural abnormalities in the prefrontal cortex of psychiatric disorders. Mol Psychiatry 2008 [Epub ahead of print].
21. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A 1998;**95**:13290–13295.
22. Rajkowska G. Cell pathology in mood disorders. Semin Clin Neuropsychiatry 2002;**7**:281–292.
23. Tkachev D, Mimmack ML, Ryan MM et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003;**362**:798–805.
24. Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V, Rachmanova V. Electron microscopy of oligodendroglia in severe mental illness. Brain Res Bull 2001;**55**:597–610.
25. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res 2004;**67**:269–275.
26. Vostrikov VM, Uranova NA, Orlovskaya DD. Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. Schizophr Res 2007;**94**:273–280.
27. Amaral DG, Price JL. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J Comp Neurol 1984;**230**:465–496.
28. Anand BK, Malhotra CL, Singh B, Dua S. Cerebellar projections to limbic system. J Neurophysiol 1959;**22**: 451–457.
29. Heath RG, Dempesy CW, Fontana CJ, Myers WA. Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats. Biol Psychiatry 1978;**13**:501–529.
30. Morecraft RJ, Geula C, Mesulam MM. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 1992;**323**:341–358.
31. Nauta WJ. The problem of the frontal lobe: a reinterpretation. J Psychiatr Res 1971;**8**:167–187.
32. Ramnani N. The primate cortico-cerebellar system: anatomy and function. Nat Rev Neurosci 2006;**7**:511–522.
33. Snider RS, Maiti A. Cerebellar contributions to the Papez circuit. J Neurosci Res 1976;**2**:133–146.
34. Cavanagh JT, Van Beck M, Muir W, Blackwood DH. Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. Br J Psychiatry 2002;**180**:320–326.
35. Deckersbach T, Savage CR, Reilly-Harrington N, Clark L, Sachs G, Rauch SL. Episodic memory impairment in bipolar disorder and obsessive-compulsive disorder: the role of memory strategies. Bipolar Disord 2004;**6**:233–244.
36. Glahn DC, Bearden CE, Caetano S et al. Declarative memory impairment in pediatric bipolar disorder. Bipolar Disord 2005;**7**:546–554.
37. Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, Herbener ES, Sweeney JA. Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. Am J Psychiatry 2006;**163**: 286–293.
38. Wolfe J, Granholm E, Butters N, Saunders E, Janowsky D. Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. J Affect Disord 1987;**13**:83–92.
39. Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 1996;**6**:228–236.

https://doi.org/10.1111/j.1601-5215.2009.00414.x Published online by Cambridge University Press

40. Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, Smeraldi E. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. Am J Med Genet B Neuropsychiatr Genet 2003;**123B**:23–26.
41. Mitterauer B. Clock genes, feedback loops and their possible role in the etiology of bipolar disorders: an integrative model. Med Hypotheses 2000;**55**:155–159.
42. Steeves TD, King DP, Zhao Y et al. Molecular cloning and characterization of the human CLOCK gene: expression in the suprachiasmatic nuclei. Genomics 1999;**57**: 189–200.
43. Drevets WC, Price JL, Simpson JR Jr et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;**386**:824–827.
44. Blumberg HP, Krystal JH, Bansal R et al. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. Biol Psychiatry 2006;**59**:611–618.
45. Doris A, Belton E, Ebmeier KP, Glabus MF, Marshall I. Reduction of cingulate gray matter density in poor outcome bipolar illness. Psychiatry Res 2004;**130**:153–159.
46. Fornito A, Malhi GS, Lagopoulos J et al. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. Psychiatry Res 2008;**162**:123–132.
47. Lopez-Larson MP, Delbello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol Psychiatry 2002;**52**:93–100.
48. Lyoo IK, Kim MJ, Stoll AL et al. Frontal lobe gray matter density decreases in bipolar I disorder. Biol Psychiatry 2004;**55**:648–651.
49. Lyoo IK, Sung YH, Dager SR et al. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord 2006;**8**: 65–74.
50. Nugent AC, Milham MP, Bain EE et al. Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. Neuroimage 2006;**30**:485–497.
51. Adler CM, Delbello MP, Jarvis K, Levine A, Adams J, Strakowski SM. Voxel-based study of structural changes in first-episode patients with bipolar disorder. Biol Psychiatry 2007;**61**:776–781.
52. Frazier JA, Breeze JL, Makris N et al. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. Bipolar Disord 2005;**7**:555–569.
53. Kalmar JH, Wang F, Spencer L et al. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. J Int Neuropsychol Soc 2009;**15**:476–481.
54. Kaur S, Sassi RB, Axelson D et al. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. Am J Psychiatry 2005;**162**:1637–1643.
55. Najt P, Nicoletti M, Chen HH et al. Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. Neurosci Lett 2007;**413**: 183–186.
56. Wilke M, Kowatch RA, Delbello MP, Mills NP, Holland SK. Voxel-based morphometry in adolescents with bipolar disorder: first results. Psychiatry Res 2004;**131**:57–69.
57. Dickstein DP, Milham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, Leibenluft E. Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. Arch Gen Psychiatry 2005;**62**:734–741.
58. Sanches M, Sassi RB, Axelson D et al. Subgenual prefrontal cortex of child and adolescent bipolar patients: a morphometric magnetic resonance imaging study. Psychiatry Res 2005;**138**:43–49.
59. Blumberg HP, Kaufman J, Martin A, Charney DS, Krystal JH, Peterson BS. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. Ann N Y Acad Sci 2004;**1021**:376–383.
60. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 2000;**48**:740–754.
61. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. Lancet 2000;**356**:1241–1242.
62. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 2001;**11**:240–249.
63. Sassi RB, Nicoletti M, Brambilla P et al. Increased gray matter volume in lithium-treated bipolar disorder patients. Neurosci Lett 2002;**329**:243–245.
64. Monkul ES, Matsuo K, Nicoletti MA et al. Prefrontal gray matter increases in healthy individuals after lithium treatment: a voxel-based morphometry study. Neurosci Lett 2007;**429**:7–11.
65. Bearden CE, Thompson PM, Dalwani M et al. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol Psychiatry 2007;**62**:7–16.
66. Altshuler LL, 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**:663–664.
67. Blumberg HP, Kaufman J, Martin A et al. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry 2003;**60**:1201–1208.
68. Pearlson GD, Barta PE, Powers RE et al. Ziskind-Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol Psychiatry 1997;**41**:1–14.
69. Strakowski SM, Delbello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, Larson ER. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999;**56**:254–260.
70. Scherk H, Gruber O, Menzel P et al. 5-HTTLPR genotype influences amygdala volume. Eur Arch Psychiatry Clin Neurosci 2009;**259**:212–217.
71. Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;**44**:565–573.
72. Chen BK, Sassi R, Axelson D et al. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. Biol Psychiatry 2004;**56**:399–405.
73. Delbello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord 2004;**6**:43–52.

https://doi.org/10.1111/j.1601-5215.2009.00414.x Published online by Cambridge University Press

74. Foland LC, Altshuler LL, Sugar CA et al. Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium. Neuroreport 2008;**19**: 221–224.
75. Bearden CE, Soares JC, Klunder AD et al. Three-dimensional mapping of hippocampal anatomy in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2008;**47**:515–525.
76. Frazier JA, Chiu S, Breeze JL et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005;**162**:1256–1265.
77. Altshuler LL, Bartzokis G, Grieder T et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry 2000;**48**:147–162.
78. Hauser P, Matochik J, Altshuler LL, Denicoff KD, Conrad A, Li X, Post RM. MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. J Affect Disord 2000;**60**:25–32.
79. Hirayasu Y, Shenton ME, Salisbury DF et al. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am J Psychiatry 1998;**155**:1384–1391.
80. Noga JT, Vladar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res 2001;**106**:25–34.
81. Swayze VW II, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. Biol Psychiatry 1992;**31**:221–240.
82. Velakoulis D, Pantelis C, Mcgorry PD et al. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch Gen Psychiatry 1999;**56**:133–141.
83. Chepenik LG, Fredericks C, Papademetris X et al. Effects of the brain-derived neurotrophic growth factor val66met variation on hippocampus morphology in bipolar disorder. Neuropsychopharmacology 2009;**34**:944–951.
84. Mcintosh AM, Moorhead TW, Mckirdy J et al. Temporal grey matter reductions in bipolar disorder are associated with the BDNF Val66Met polymorphism. Mol Psychiatry 2007;**12**:902–903.
85. Hwang J, Lyoo IK, Dager SR et al. Basal ganglia shape alterations in bipolar disorder. Am J Psychiatry 2006;**163**:276–285.
86. Strakowski SM, Adler CM, Delbello MP. Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? Bipolar Disord 2002;**4**:80–88.
87. Delbello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology 1999;**21**:63–68.
88. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. Am J Psychiatry 2005;**162**:1530–1532.
89. Monkul ES, Hatch JP, Sassi RB et al. MRI study of the cerebellum in young bipolar patients. Prog Neuropsychopharmacol Biol Psychiatry 2008;**32**:613–619.
90. Brambilla P, Harenski K, Nicoletti M et al. MRI study of posterior fossa structures and brain ventricles in bipolar patients. J Psychiatr Res 2001;**35**:313–322.
91. Altshuler LL, Bookheimer SY, Townsend J et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. Biol Psychiatry 2005;**58**:763–769.
92. Blumberg HP, Leung HC, Skudlarski P et al. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. Arch Gen Psychiatry 2003;**60**:601–609.
93. Blumberg HP, Stern E, Ricketts S et al. Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. Am J Psychiatry 1999;**156**:1986–1988.
94. Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biol Psychiatry 2004;**55**:1163–1170.
95. Rubinsztein JS, Fletcher PC, Rogers RD et al. Decision-making in mania: a PET study. Brain 2001;**124**:2550–2563.
96. Chen CH, Lennox B, Jacob R et al. Explicit and implicit facial affect recognition in manic and depressed States of bipolar disorder: a functional magnetic resonance imaging study. Biol Psychiatry 2006;**59**:31–39.
97. Lawrence NS, Williams AM, Surguladze S et al. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry 2004;**55**:578–587.
98. Blumberg HP, Donegan NH, Sanislow CA et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology (Berl) 2005;**183**:308–313.
99. Kronhaus DM, Lawrence NS, Williams AM et al. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disord 2006;**8**:28–39.
100. Kruger S, Seminowicz D, Goldapple K, Kennedy SH, Mayberg HS. State and trait influences on mood regulation in bipolar disorder: blood flow differences with an acute mood challenge. Biol Psychiatry 2003;**54**:1274–1283.
101. Kruger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg HS. Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. Am J Psychiatry 2006;**163**:257–264.
102. Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R. An emotional Stroop functional MRI study of euthymic bipolar disorder. Bipolar Disord 2005; **7**(Suppl. 5):58–69.
103. Blumberg HP, Martin A, Kaufman J et al. Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. Am J Psychiatry 2003;**160**:1345–1347.
104. Leibenluft E, Rich BA, Vinton DT et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 2007;**164**: 52–60.
105. Pavuluri MN, O'connor MM, Harral E, Sweeney JA. Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. Biol Psychiatry 2007;**62**:158–167.
106. Rich BA, Vinton DT, Roberson-Nay R et al. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proc Natl Acad Sci U S A 2006;**103**:8900–8905.

https://doi.org/10.1111/j.1601-5215.2009.00414.x Published online by Cambridge University Press

107. Jogia J, Haldane M, Cobb A, Kumari V, Frangou S. Pilot investigation of the changes in cortical activation during facial affect recognition with lamotrigine monotherapy in bipolar disorder. Br J Psychiatry 2008;**192**:197–201.
108. Shah MP, Wang F, Kalmar JH et al. Role of variation in the Serotonin Transporter Protein Gene (SLC6A4) in trait disturbances in the ventral anterior cingulate in bipolar disorder. Neuropsychopharmacology 2009;**34**:1301–1305.
109. Altshuler L, Bookheimer S, Proenza MA et al. Increased amygdala activation during mania: a functional magnetic resonance imaging study. Am J Psychiatry 2005;**162**:1211–1213.
110. Chang KD, Wagner C, Garrett A, Howe M, Reiss A. A preliminary functional magnetic resonance imaging study of prefrontal-amygdalar activation changes in adolescents with bipolar depression treated with lamotrigine. Bipolar Disord 2008;**10**:426–431.
111. Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME. Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. Pharmacol Biochem Behav 2002;**71**:431–447.
112. Ketter TA, Kimbrell TA, George MS et al. Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. Biol Psychiatry 2001;**49**:97–109.
113. Mah L, Zarate CA Jr, Singh J, Duan YF, Luckenbaugh DA, Manji HK, Drevets WC. Regional cerebral glucose metabolic abnormalities in bipolar II depression. Biol Psychiatry 2007;**61**:765–775.
114. Malhi GS, Lagopoulos J, Ward PB et al. Cognitive generation of affect in bipolar depression: an fMRI study. Eur J Neurosci 2004;**19**:741–754.
115. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord 2000;**2**:237–248.
116. Krystal JH, Sanacora G, Blumberg H et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol Psychiatry 2002;**7**(Suppl. 1):S71–S80.
117. Braga MF, Aroniadou-Anderjaska V, Post RM, Li H. Lamotrigine reduces spontaneous and evoked GABAA receptor-mediated synaptic transmission in the basolateral amygdala: implications for its effects in seizure and affective disorders. Neuropharmacology 2002;**42**:522–529.
118. Tian LM, Alkadhi KA. Valproic acid inhibits the depolarizing rectification in neurons of rat amygdala. Neuropharmacology 1994;**33**:1131–1138.
119. Blumberg HP, Stern E, Martinez D et al. Increased anterior cingulate and caudate activity in bipolar mania. Biol Psychiatry 2000;**48**:1045–1052.
120. Caligiuri MP, Brown GG, Meloy MJ et al. An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. Psychiatry Res 2003;**123**:171–182.
121. Malhi GS, Lagopoulos J, Sachdev P, Mitchell PB, Ivanovski B, Parker GB. Cognitive generation of affect in hypomania: an fMRI study. Bipolar Disord 2004;**6**:271–285.
122. Goodwin GM, Cavanagh JT, Glabus MF, Kehoe RF, O'carroll RE, Ebmeier KP. Uptake of 99mTc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients: associations with mania. Br J Psychiatry 1997;**170**:426–430.
123. Malhi GS, Lagopoulos J, Owen AM, Ivanovski B, Shnier R, Sachdev P. Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. J Affect Disord 2007;**97**:109–122.
124. Strakowski SM, Adler CM, Holland SK, Mills NP, Delbello MP, Eliassen JC. Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. Am J Psychiatry 2005;**162**:1697–1705.
125. Loeber RT, Gruber SA, Cohen BM, Renshaw PF, Sherwood AR, Yurgelun-Todd DA. Cerebellar blood volume in bipolar patients correlates with medication. Biol Psychiatry 2002;**51**:370–376.
126. Atmaca M, Ozdemir H, Yildirim H. Corpus callosum areas in first-episode patients with bipolar disorder. Psychol Med 2007;**37**:699–704.
127. Coffman JA, Bornstein RA, Olson SC, Schwarzkopf SB, Nasrallah HA. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biol Psychiatry 1990;**27**:1188–1196.
128. Haznedar MM, Roversi F, Pallanti S et al. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. Biol Psychiatry 2005;**57**:733–742.
129. Brambilla P, Nicoletti MA, Sassi RB et al. Magnetic resonance imaging study of corpus callosum abnormalities in patients with bipolar disorder. Biol Psychiatry 2003;**54**:1294–1297.
130. Brambilla P, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Keshavan MS, Soares JC. Corpus callosum signal intensity in patients with bipolar and unipolar disorder. J Neurol Neurosurg Psychiatry 2004;**75**:221–225.
131. Caetano SC, Silveira CM, Kaur S et al. Abnormal corpus callosum myelination in pediatric bipolar patients. J Affect Disord 2008;**108**:297–301.
132. Schmahmann JD, Pandya DN. Fiber pathways of the brain. New York: Oxford University Press, 2006.
133. Beaulieu C. The basis of anisotropic water diffusion in the nervous system–a technical review. NMR Biomed 2002;**15**:435–455.
134. Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, Strakowski SM. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. Bipolar Disord 2004;**6**:197–203.
135. Adler CM, Adams J, Delbello MP et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. Am J Psychiatry 2006;**163**:322–324.
136. Beyer JL, Taylor WD, Macfall JR et al. Cortical white matter microstructural abnormalities in bipolar disorder. Neuropsychopharmacology 2005;**30**:2225–2229.
137. Bruno S, Cercignani M, Ron MA. White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. Bipolar Disord 2008;**10**:460–468.
138. Houenou J, Wessa M, Douaud G et al. Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. Mol Psychiatry 2007;**12**:1001–1010.

139. Regenold WT, D'agostino CA, Ramesh N, Hasnain M, Roys S, Gullapalli RP. Diffusion-weighted magnetic resonance imaging of white matter in bipolar disorder: a pilot study. Bipolar Disord 2006;**8**:188–195.
140. Versace A, Almeida JR, Hassel S et al. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Arch Gen Psychiatry 2008;**65**: 1041–1052.
141. Wang F, Kalmar JH, Edmiston E et al. Abnormal corpus callosum integrity in bipolar disorder: a diffusion tensor imaging study. Biol Psychiatry 2008;**64**:730–733.
142. Wang F, Jackowski M, Kalmar JH et al. Abnormal anterior cingulum integrity in bipolar disorder determined through diffusion tensor imaging. Br J Psychiatry 2008;**193**:126–129.
143. Kalmar JH, Wang F, Chepenik LG et al. Relation between amygdala structure and function in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2009;**48**:636–642.
144. Wang F, Kalmar JH, He Y et al. Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. Biol Psychiatry 2009;**66**:516–521.

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