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Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala–anterior paralimbic neural system

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Abstract

Objectives—In past decades, neuroimaging research in bipolar disorder has demonstrated a convergence of findings in an amygdala–anterior paralimbic cortex neural system. This paper reviews behavioral neurology literature that first suggested a central role for this neural system in the disorder and the neuroimaging evidence that supports it.

Methods—Relevant articles are reviewed to provide an amygdala–anterior paralimbic cortex neural system model of bipolar disorder, including articles from the fields of behavioral neurology and neuroanatomy, and neuroimaging.

Results—The literature is highly supportive of key roles for the amygdala, anterior paralimbic cortices, and connections among these structures in the emotional dysregulation of bipolar disorder. The functions subserved by their more widely distributed connection sites suggest that broader system dysfunction could account for the range of functions—from neurovegetative to cognitive—disrupted in the disorder. Abnormalities in some components of this neural system are apparent by adolescence, while others, such as those in rostral prefrontal regions, appear to progress over adolescence and young adulthood, suggesting a neurodevelopmental model of the disorder. However, some findings conflict, which may reflect the small sample sizes of some studies, and clinical heterogeneity and methodological differences across studies.

Conclusions—Consistent with models derived from early behavioral neurology studies, neuroimaging studies support a central role for an amygdala–anterior paralimbic neural system in bipolar disorder, and implicate abnormalities in the development of this system in the disorder. This system will be an important focus of future studies on the developmental pathophysiology, detection, treatment, and prevention of the disorder.

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Keywords

amygdala; bipolar disorder; prefrontal cortex

Overview

Neuroimaging research over the past several decades has yielded a convergent view of bipolar disorder (BD) that supports a central role for an amygdala–anterior paralimbic cortex neural system in the disorder. This model draws from early behavioral neurology reports of lesions in anterior paralimbic cortices and seizure foci in mesial temporal structures, such as the amygdala, in patients whose symptoms were similar to those of individuals with primary mood disorders. It also draws from neuroanatomic and neurobehavioral studies, which identified connections among the amygdala and anterior paralimbic structures, including the ventral prefrontal cortex (VPFC), insular cortex (IC), and temporopolar cortex (TPC), and the central role of this system of interconnected structures in emotional regulation. These studies also identified more widely distributed connection sites of this system including more rostral, dorsal and lateral prefrontal cortices (PFC), hippocampus, striatum, thalamus, cerebellum and hypothalamus (1–5). Together, the structures of this system subserve the phylogenetically broad range of functions characteristically disrupted in BD, from basic biological rhythm and neurovegetative processes, such as sleep and appetitive functions, to motivated behaviors and thought processes. These considerations suggest that impaired amygdala–anterior paralimbic functioning could contribute not only to the emotional dysregulation of BD, but also to the broader range of symptoms characteristic of acute mood episodes through disruption of the larger neural system.

Structural and functional neuroimaging studies focusing on regional abnormalities have provided converging evidence supporting involvement of this system in BD, with the strongest evidence for abnormalities within the amygdala and VPFC. Abnormalities within each of the connection sites above have also been reported; although the hypothalamus has been relatively elusive given limitations of current neuroimaging technologies.

In the past few years, implementation of new research techniques has provided data on connections between structures within this neural system in BD. Studies employing imaging methods such as diffusion tensor imaging (DTI), and functional connectivity analysis of functional magnetic resonance imaging (fMRI) data, have provided evidence to suggest important roles for both structural and functional connectivity abnormalities in the disorder.

This article will review behavioral neurological and neuroanatomical studies that informed the neural system model of BD, the structural and functional neuroimaging studies that support abnormalities within the implicated regions, and more recent neuroimaging studies that support abnormalities within the connections among these regions. Studies that have contributed to a view of BD as a developmental disorder of this neural system will be reviewed, including evidence that abnormalities in subcortical limbic and paralimbic cortices appear to be established by adolescence, whereas differences in more rostral PFC areas may progress during adolescence and young adulthood. This article will also touch upon findings from genetic, postmortem histopathological, and neuropsychological studies that may inform understanding of the mechanisms that underlie the neural system findings.

A model based on behavioral neuroanatomical and neurological studies

Clinical reports of BD-type symptoms in patients who sustained brain lesions, dating back at least to the 19th century, implicated impairment in the VPFC in BD. These reports included descriptions of impaired motivation and depressive symptoms, as well as inappropriate

euphoria, irritability, distractibility, excessive psychomotor behavior, hypersexuality, grandiosity, and paranoia (6–14). Subsequent investigations of the VPFC have provided a more nuanced view of how dysfunction in VPFC, and associated regions, might manifest as BD symptomatology. The VPFC appears to play a central role in the ability to rapidly adapt behavior in the face of changes in positive and negative environmental contingencies (14). If the VPFC is injured, an individual still may be able to articulate the optimal behavior given a particular situation; however, when within an emotionally- or motivationally-charged situation, that individual cannot adaptively regulate behavior, leading to actions that can have negative consequences (6, 11, 15, 16). Thus, impaired VPFC regulation of behavior could lead to manic-type behaviors, including excessive involvement in hedonically-driven activities such as sexual indiscretions, gambling, and excessive spending. The VPFC also performs a critical role in integrating the motivational relevance of sensory information from the environment with that from the internal milieu, and then providing regulatory feedback to structures such as the amygdala and hypothalamus, thereby influencing emotional as well as neurovegetative functions (17). For example, the processing of facial expressions of others, which has high intrinsic motivational relevance, relies heavily upon VPFC, amygdala, and their interconnections (18) and is disrupted in both youths and adults with BD (19–23). Such disturbances could cause misinterpretations of social cues and altered responses to social situations (18, 24). Together, these observations suggest an important role for the VPFC, its limbic subcortical connection sites, and the connectivity between them, in difficulties in emotional regulation, adaptive behavioral regulation, and social behavior, such as those present in BD.

The influence of the hemispheric laterality of frontal deficits described in the lesion literature was also an early source of inspiration for hypotheses about the brain bases of BD symptomatology. The left hemisphere has been theorized to be more involved in the processing of positive emotional states and approach behaviors, whereas the right hemisphere is more involved in negative emotional states and withdrawal behaviors. A frontal lesion in one hemisphere appears to lead to a relative disinhibition of the activity of the other (25–27), such that left frontal lesions have been associated more with depressive symptoms, whereas manic symptoms, although relatively much less common, have been reported more in association with right frontal lesions (26).

In the latter half of the 20th century, observations of BD-type symptoms in patients with seizure disorders suggested that excessive activity in mesial temporal lobe structures might contribute to mood symptomatology in BD. Patients with complex partial seizure disorders with mesial temporal foci (8, 28, 29) were observed to have both depressive and elevated mood symptoms, as well as psychotic symptoms. The valence and course of affective symptoms also appeared to be influenced by hemispheric laterality. Humorlessness, fear, and paranoia were more associated with left-sided foci; whereas elation, emotionality, circumstantiality, as well as a fluctuating manic-depressive type course were more associated with right-sided foci (28, 29). These reports implicated excessive activity in mesial temporal structures, such as the amygdala, in BD. Post et al. (30) drew parallels between epileptic patients with mesial temporal foci who are at increased risk for future seizures, as these limbic structures are vulnerable to sensitization, and BD patients who have a decreased threshold for mood episodes after untreated episodes. These observations were part of the basis for the first treatment trials of anticonvulsants, now an important class of pharmacotherapy for BD. Preliminary functional neuroimaging findings suggest that anticonvulsants may indeed help to normalize mesial temporal activity in the disorder (31).

The findings that abnormalities in both VPFC and mesial temporal structures, which share substantial reciprocal inhibitory connections, could result in BD-type symptoms led to investigations into whether abnormalities within these structures or in the integrity of their

connections could contribute to BD. As the understanding grew that neural functions are often subserved by distributed neural systems, rather than by single regions of the brain, a neural systems model for BD emerged. Increasing evidence supported the idea that if a node within the system is disrupted, the resulting disruption in functioning of the system could result in BD-type symptoms. Consistent with this view, lesions within striatum, thalamus, and cerebellum (32, 33), regions that share significant anatomic interconnections with VPFC and the mesial temporal lobe (1–5), were also associated with BD-type symptoms. Mayberg and others asserted a neural systems model of mood disorders in which anterior paralimbic dysfunction, within VPFC and TPC, might be an important common endpoint critical in the generation of the mood disorders (34–36).

Recent evidence, as reviewed subsequently, is mounting for an important role for abnormalities within the connections themselves within the neural system of BD. The importance of these connections in disordered mood is not a new idea. For example, early in the 20th century, Starr (37) noted altered emotional regulation associated with lesions in intrahemispheric frontal-subcortical connections as well as interhemispheric connections of the corpus callosum. Symptoms in the patients included “undue excitement, causeless laughter, unusual crying, great depression and a lack of harmony between the association of ideas and the states of feeling which they should awaken.” Connections between anterior cingulate and more rostral PFC with subcortical structures were also the targets of psychosurgical procedures for refractory mood and anxiety disorders of the early 20th century (38). Recent evidence implicating pathology within the white matter connections in BD includes findings from genetic studies suggesting association of BD with genes that regulate the development and plasticity of connections, as well as postmortem studies of BD that demonstrate frontal reductions in glia, and especially oligodendrocytes, as well as down-regulation of oligodendrocyte- and myelination-related genes (39–45).

Evidence that the timing of lesions within nodes of the neural system may also be critical to the resulting behavioral phenotypes suggests a neurodevelopmental model for BD. For example, studies of non-human primates suggest that early amygdala lesions could lead to disinhibited social interactions and hyperactivity (46, 47). In humans, individuals with amygdala lesions in youth demonstrate abnormalities in emotional processing, responses, and interactions (48, 49), whereas individuals with amygdala lesions in adulthood do not show as pronounced difficulties (50). This observation suggests that early amygdala abnormalities can be especially potent in contributing to emotional processing abnormalities that have been reported in youths and adults with BD (21). Evidence also supports the importance of the activity of inputs to a developing brain region (51–53). For example, early amygdala lesions in animal models have been associated with abnormalities in the development of its PFC projection regions (54, 55), and the striatum (56). These findings suggest that early amygdala abnormalities may also influence the development of other regions implicated in the disorder. As the amygdala shares especially dense connections with olfactocentric paralimbic cortices (OPC), which include the orbitofrontal, temporopolar, and insular cortices, we suggested a model in which it may have particular effects on the OPC, in addition to other amygdala projection regions.

Summary of functional neuroanatomical and behavioral neurological studies

In summary, behavioral neurological, functional neuroanatomical, and postmortem studies implicate an amygdala–anterior paralimbic neural system in BD. Although VPFC deficits and excessive amygdala activity emerge as abnormalities that are especially implicated, evidence suggests that abnormalities at many nodes within this system, as well as within the connections between nodes, are also capable of producing BD-type symptoms. Early dysfunction in an individual node could have implications for the development of the neural system as a whole, such as the effects of early abnormalities in amygdala inputs on the

development of other aspects of the system. Moreover, dysfunction generated in the more widely distributed system may be necessary for the expression of the full BD phenotype. For example, neurovegetative symptoms that may relate to dysregulated hypothalamic functioning are important components of the disorder. In fact, sleep disturbances often herald, and may be important in generating, the switches to acute mood states in BD (57). Neuropsychological testing suggested that changes in the relative dominance of the left or right PFC might contribute to vulnerability to either elevated or depressed acute mood states of BD (58).

Structural imaging findings

Amygdala

Volume abnormalities in amygdala are among the most reported findings in BD. However, studies conflict as to whether the volume abnormalities detected are increases or decreases. The direction of findings appears to vary more in adults (59–62), whereas findings of decreases in amygdala volumes in adolescents with BD are one of the more consistent findings in the disorder (60, 63–68).

Possible interpretations for the differences in the direction of findings in adults include the possibility that volume decreases in the amygdala are an early feature of BD and that factors such as further development, episodes, or exposures (such as to medication) may contribute to increases in adults. For example, a recent study provided evidence for differences in the trajectory of volume increases of the amygdala in adolescents with BD when compared to healthy adolescents (69). Mood-stabilizing medications may be protective. Postmortem studies of amygdala volume in BD show significant glial reduction in only those BD patients not treated with lithium or valproate (70), and the medications have been found to be associated with larger volume of the amygdala (63, 71). However, it is also possible that adolescent-onset BD may comprise a more homogeneous subgroup with the illness, which may bear a distinctive neuroanatomic footprint. Studies of adults with BD may vary in the proportion of subjects with adolescent-onset illness. Differences in volumes of the amygdala may also point to other clinically interesting subgroups within BD. For instance, genetic variations, e.g., within the serotonin transporter promoter protein (5-HTTLPR) (72), as well as stress exposure (73), have been shown to affect amygdala morphology. Understanding of this heterogeneity has been limited by the relatively small sample sizes of studies. Studies with larger sample sizes with power to systematically assess these factors are needed.

Anterior paralimbic cortices

Volume decreases in anterior paralimbic cortices are also consistently reported neuroimaging findings in BD. A seminal report published in 1997 by Drevets et al. (74) identified gray matter volume decreases in subgenual PFC in adults with BD. Subsequent studies were consistent with these findings, as well as findings of volume abnormalities extending to other VPFC regions that include more rostral and lateral regions (68, 75–87). These findings are consistent with postmortem studies showing cellular decreases in these regions and that suggest that glial pathology may be important in these volume decreases (41, 42). A possible role for VPFC morphology in vulnerability to cycling in BD is suggested by smaller VPFC volumes in adults with BD with rapid-cycling than in adults without, although it is also possible that the increased number of episodes that accumulate in such patients could have had deleterious effects on the VPFC (76).

In adolescents, volume findings in VPFC regions have been more variable and include negative findings (66, 68, 75, 76, 80–82, 86, 88, 89). The variation may be due, at least in part, to methodological differences across studies such as the VPFC subregions that were the focus of the studies and the anatomical boundaries used to define them. Subregions

compared varied from subsections of orbitofrontal cortex (OFC) through ventrolateral or rostral PFC or anterior cingulate to volumes of the entire frontal lobe. However, variability in findings across studies may also relate to dynamic developmental changes in cortical regions occurring during adolescence. This development may further vary by gender (90), and analyses of youth with BD have shown VPFC volume is influenced by gender (86). Thus, the variability among studies in the developmental stage and gender of the adolescents included in the investigations could have influenced the ability to detect differences that may progress during adolescence.

Consistent with the developmental theory previously discussed, a recent voxel-based whole brain analysis of 118 adolescents, 41 with BD and 77 without, showed gray matter volume decreases in OPC (91). The OPC structures share cytoarchitectural features and are thought to develop in concert (3, 4). The finding of decreased volume in this grouping of structures in adolescents with BD suggests that further understanding of the development of these cortices may hold important clues about the developmental pathophysiology of BD.

There is a paucity of longitudinal studies of youths with BD to inform understanding of the trajectory of development of morphological differences in BD. A longitudinal study of youths at risk for BD showed ventral anterior cingulate cortex (VACC) decreases only after the first episode of mania (92), suggesting that the decreases might be associated with vulnerability to onset of acute episodes, although it is possible that the episodes cause the decreases. A small study of adolescents and young adults with BD, rescanned after approximately a two-year period, showed larger decreases in volume than in healthy comparison (HC) subjects in more rostral regions of PFC (81). This suggests that there may be a development-related progression in the emergence of cortical abnormalities in BD, with earlier OPC abnormalities followed by progressive abnormalities in more rostral heteromodal PFC regions (81, 91, 93). Cross-sectional studies of BD and HC adults conflict as to whether VPFC volumes change further during the course of adulthood (76, 94); future longitudinal studies will be helpful to address this issue.

Associated structures

Hippocampus—The hippocampus has been a focus of many imaging studies of BD, given its mesial temporal location and role in emotional and mnemonic processes implicated in the disorder; however, morphological findings in the hippocampus have been quite variable. Studies of both adults and adolescents have included findings of decreases, as well as negative reports (59–63, 95–103). Discrepant findings could be related to methodological differences across studies. For example, as volume decreases may be localized to certain hippocampus subregions (96), different methods of delineating the structure may yield varying results. Variability across studies could also relate to the substantial plasticity of the hippocampus through adulthood, which can be highly influenced by sex hormones, developmental factors, genetic variations, stress, and treatment (96, 97, 104, 105). For example, in a study of preadolescents and adolescents with BD, Frazier et al. (97) noted that hippocampus volumes were decreased only in the girls, suggesting the possibility of sexually dimorphic development of the hippocampus in BD. Developmental effects are also implicated by a study that showed age-related increases in hippocampus volumes in youths with BD not observed in healthy youths (96). Genetic factors have also been a topic of recent interest. Findings that brain-derived neurotrophic growth factor (BDNF) has potent neurotrophic effects in the hippocampus (106), and that the BDNF *Val66Met* polymorphic variation may be associated with subtypes of BD (107, 108), prompted studies of influences of this variation on the hippocampus in BD. Chepenik et al. (104) found decreases in hippocampus volumes in adults with BD that were more pronounced in individuals carrying the *Met* allele. Another research group performed a four-year longitudinal study of adults

with BD and found that individuals with BD carrying the *Met* allele had larger decreases in hippocampus volume over time (105), suggesting that the presence of this genetic variation might have ongoing effects throughout adulthood. Treatment of BD may have salutary effects on hippocampal volume, with increases observed in patients with BD taking lithium salts (71, 96). Taken together, these data suggest that hippocampus involvement in BD may vary by subgroups of gender or genetic variation and may be a particularly dynamic region within the neural system of BD, sensitive to influences such as stress and treatment.

Striatum and thalamus—There have been relatively few studies of the striatum and thalamus in BD. Given the central role of abnormalities in motivation in acute mood states of BD, with increases in motivationally-driven behaviors in mania and amotivation and behavioral constriction in depression, abnormalities in the ventral striatum are highly implicated in the disorder. However, this region has been difficult to study owing to methodological challenges, such as in delineating ventral striatal boundaries. A whole brain voxel-based study of preadolescents and adolescents with BD did demonstrate gray matter reductions in the region of the accumbens (66). Some studies have examined the basal ganglia more grossly and reported differences in volume or shape, particularly if the subjects were not taking medications (65, 109, 110). Given the prominent changes in motivation in the disorder, we anticipate that as improved methods to study the ventral striatum emerge, these may increasingly reveal ventral striatal involvement in the disorder. Studies of thalamic volume in BD are also relatively rare and have yielded varying results (75, 97); the heterogeneity of thalamic nuclei and the difficulty of isolating those with the most interconnections to the amygdala–anterior paralimbic system (such as the anterior and dorsomedial nuclei) using current methods has made this, too, a challenging region to study.

Cerebellum—The cerebellum has anatomical connections to the amygdala–anterior paralimbic system (111–114). The role of the cerebellum, and particularly of the vermis, in emotional behaviors is increasingly recognized, and individuals with cerebellar lesions have been noted to have BD-type symptoms (33, 115–119). DelBello et al. pioneered neuroimaging work in the cerebellum in BD, demonstrating volume abnormalities in the cerebellar vermis associated with the number of prior affective episodes (120–122) as well as family history of BD (123). Vermis volume differences in BD have also been suggested to have sexually dimorphic features (124).

Summary of structural neuroimaging findings of BD

Consistent with early behavioral neurology models, structural neuroimaging studies of BD converged in demonstrating volume abnormalities in the amygdala and anterior paralimbic structures, as well as in some of the associated regions. Postmortem studies implicate glial pathology in these changes. Some abnormalities, including decreased volume in amygdala and OPC may already be present by adolescence, with amygdala volume decreases being especially consistent findings (60, 63–68). Rostral frontal abnormalities may continue to progress during adolescence and young adulthood, to become more prominent in adults with the disorder. Age of onset, sex, genetic variations, and pharmacotherapy may influence morphology, contributing to heterogeneity in the disorder and to variable findings across some studies, highlighting the need for larger studies in which these factors can be systematically assessed.

Functional imaging findings

Amygdala

As in the structural neuroimaging research, the amygdala has been a focus of functional neuroimaging investigations of BD. As predicted by the behavioral neurology models,

increased amygdala activity is a relatively consistent finding in functional neuroimaging studies of BD, reported in adolescents and adults both at rest and during emotional tasks, and across mood states (31, 125–137), suggesting that amygdala dysfunction may be a trait feature of BD. However, there have been studies that have not found increases in individuals with BD while euthymic, suggesting that amygdala responses may show excessive increases with acute mood states (125, 138, 139). One intriguing possibility is that amygdala increases may be diminished by pharmacotherapy. For example, consistent with the effects of anticonvulsants predicted by the seizure model above, a small cross sectional study suggested that elevated amygdala responses in BD are diminished by treatment, particularly with anticonvulsants (31). We speculate that anticonvulsants may have these effects through restoration of homeostatic balance between the excitatory glutamate and inhibitory gamma amino butyric acid (GABA) inputs (31, 140–142).

Studies are beginning to emerge that integrate both structural and functional neuroimaging methods to study BD; these have potential to suggest mechanisms that underlie neural system findings. For instance, a study by Kalmar et al. (130), of both amygdala structure and function in the same adolescents with BD, showed an association between volume decreases and heightened responses to emotional stimuli, such that the smaller the amygdala volume the higher the amygdala response. These findings suggest possible mechanisms such as excessive excitatory inputs to the amygdala that have deleterious cellular effects and cause volume losses, or decreases in inhibitory neurons (e.g., GABA neurons) that could contribute to amygdala disinhibition.

Postmortem studies provide supporting evidence for decreased total number of neurons and neuron density in the brains of individuals with BD. This includes neuronal findings in the lateral and accessory basal nuclei of the amygdala (143), as well as findings in several populations of inhibitory interneurons in entorhinal cortex (144, 145), parasubiculum (145), and hippocampus (146–148). There is also evidence for reduced mRNA levels of the same markers for interneurons in the hippocampus (147). Findings of decreases in inhibitory interneurons and theories of excessive excitatory inputs are not necessarily mutually exclusive, as glutamatergic neuron populations are known to interact with the inhibitory interneurons in these regions, and the interneuron populations are responsible for the downstream modulation of glutamatergic activity (146–148).

Anterior paralimbic regions

Dysfunction in VPFC regions has also been shown consistently in adults with BD. The particular subregions involved, such as VACC, medial or lateral OFC, the direction of differences, and the hemispheric lateralization of the findings appear to vary with multiple factors including mood state, medication, and various aspects of task performance. A variety of research designs have been employed, including scanning subjects at rest, as well as during many different types of activation tasks. Many of these tasks involve emotional processing, although they differ in the specific types of emotional stimuli (for example, actors' faces depicting emotions, emotionally-laden words, or autobiographical scripts), as well as task instruction such as whether the subject is explicitly told to engage with the emotional aspect of the stimuli or whether the emotional processing is implicit as the subject is instructed to perform a putatively non-emotional task, such as gender determination while viewing emotional faces. Other studies have examined performance during cognitive tasks testing attention, working memory, and the ability to inhibit prepotent responses, such as the stroop and go/no-go tasks. There are many aspects to task designs that had the potential to influence findings and could have contributed to heterogeneous findings in the literature. For example, there is some evidence that the difficulty of the task has an impact on the differential brain activation between subjects with BD and healthy subjects (149). It should also be noted that several studies, particularly the earlier functional imaging work, had small

sample sizes, increasing the possibility for false positives to introduce noise into the literature.

It is striking that, despite the variations in design across studies, consistent patterns have emerged. In adults with BD, mania has been associated with largely right-sided VPFC decreases demonstrated during performance of tasks that require processing of emotional stimuli or performance of tasks that require adaptive inhibition of responses (150–155). In depression, findings tend to be left-sided with ventral frontal increases and dorsal decreases suggesting that right-left balance, and potentially ventral-dorsal balance, influence the valence of affective episodes (132, 133, 152, 156, 157). Studies that include different mood states, or that specifically focus on euthymia, implicate VPFC dysfunction as a trait abnormality of BD (139, 152, 157–163). Perigenual ACC decreases observed across mood states, and noted to be influenced by genotype (e.g., 5-HTTLPR), suggest that some paralimbic abnormalities, such as those of the VACC, may be trait features that may be particularly prominent in genetic-based subtypes within the disorder (138). As with the amygdala above, preliminary study also suggested salutary effects of pharmacological treatment on VACC functional abnormalities (31).

Recent studies have reported dysfunction in VPFC activation in youths with BD during performance of tasks that require processing of emotional faces or inhibition of prepotent responses, suggesting that, at least for a subset of adolescents with BD, VPFC functional differences are present (135, 136, 164). However, similar to the structural imaging findings, preliminary evidence suggests that functional abnormalities in rostral PFC also progress during adolescence. For example, in a small study, rostral VPFC activation, during a task that probed adaptive inhibition of prepotent responses, increased with age in healthy adolescents but not adolescents with BD, suggesting differences in the functional development of these prefrontal cortices in adolescence in BD (165). However, drawing inferences about development from cross-sectional studies must be done with caution; longitudinal studies are needed. Functional neuroimaging studies of adults and adolescents with BD have also reported IC and TPC dysfunction (135, 166–168); however, such reports remain rare and further studies of the role of these regions in the disorder are needed.

While findings in more dorsal regions of the PFC have also been reported in BD, direct comparisons of groups with BD and with schizophrenia suggest that VPFC abnormalities may be more prominent in BD and that involvement of more dorsal and lateral PFC regions may be more prominent in schizophrenia (149, 169).

Associated regions

Hippocampus—Hippocampal dysfunction has been reported in studies of BD (131, 132, 150, 156, 170–172), detected across mood states, and especially during tasks which required the processing of negatively-valenced emotional stimuli (132, 156, 171, 172). Often the tasks did not specifically target hippocampal functions, limiting interpretation. Functional neuroimaging studies in BD that more specifically target particular aspects of hippocampus functioning are needed in order to clarify this region's role in the disorder.

Striatum and thalamus—Dysfunction in both the striatum and the thalamus has been reported in adults (131, 132, 173–176) with BD. As with the amygdala, these subcortical findings have also been reported in adolescents with BD, suggesting these abnormalities may be an early feature of the disorder (165, 177). The functional alterations have been shown in subjects at rest, as well as during performance of a wide range of tasks requiring processing of emotional stimuli, inhibition of prepotent responses, alternate types of cognitive processing, and motor function. Striatal abnormalities have been observed in BD across acute mood states and euthymia (131–133, 149, 173, 174, 176, 178–181). Several of

these studies note findings specifically in the ventral part of the striatum (131, 132, 149, 174, 181); however, studies that more specifically target ventral striatum functioning are needed.

Cerebellum—Few functional neuroimaging studies of BD have focused on function of the cerebellum. Early work demonstrates cerebellar abnormalities in adults with BD at rest (131), as well as during both emotional processing and cognitive tasks, and in individuals in both manic and euthymic states (155). Cerebellar blood flow appears to be influenced by antipsychotic treatment (182); the impact this might have on cognitive and emotional functioning has yet to be studied. As more is learned about the role of the cerebellum in emotional regulation, future studies may better target cerebellar functions. This may be a promising area for future research on BD.

Summary of functional neuroimaging studies of regional dysfunction in BD

As in the structural imaging studies, functional imaging studies of the amygdala have also been consistent, with repeated findings of abnormal amygdala activity in BD. This finding has been demonstrated in adolescents and adults, across mood states, and both at rest and during emotional tasks, suggesting that these may be early trait features of the disorder although there may be further exacerbation during acute mood episodes. Findings of an association between smaller amygdala volumes and increased activity, and studies showing that anticonvulsants may help normalize this activity, point to new hypotheses for how these abnormalities arise at a cellular level, and mechanisms that might serve as targets for treatment. There is little study of the ventral striatum, however, preliminary studies suggest that similar to amygdala, there may be both early structural and functional abnormalities.

Abnormal function in the VPFC is also consistently shown in the literature, but the direction and lateralization of findings appear to vary dynamically based on mood state and study design, and abnormalities may progress in adolescence and adulthood, especially in more rostral regions. Functional differences in associated structures such as the hippocampus have been noted, however, study designs have not frequently included methods to specifically probe functions more directly subserved by these regions; more work is needed to further clarify their contribution to the disorder.

Structural and functional connectivity

White matter connectivity

White matter abnormalities observed in structural neuroimaging studies of BD include volume decreases in frontal white matter as well as decreases in the mid-sagittal area and other abnormalities of the corpus callosum (76, 87, 183–188), supporting early lesion-based predictions of abnormalities in both the intrahemispheric frontal connections as well as interhemispheric connections in BD. DTI studies provide measures that are more sensitive to the microstructure of the white matter and its fiber organization. One of the measures principally reported is fractional anisotropy (FA), a measure of the coordinated directionality of fibers within major white matter fiber bundles (189). FA alterations have been observed in the white matter that connects VPFC to mesial temporal and striatal regions in BD (190–198). These have included findings of decreased FA in the anterior region of the cingulum bundle (197), which provides connections from caudal frontal regions to mesial temporal regions, as well as in the uncinate fasciculus, which provides important connections from the VPFC that pass through IC to terminate in amygdala and TPC regions (196). Decreases in FA in the uncinate fasciculus have been noted in the right hemisphere (196). Decreases in the anterior portions of the corpus callosum, which provides the interhemispheric connections between the left and right VPFC, have also been demonstrated in adults with BD (199, 200). Two DTI studies also detected white matter

abnormalities in youths with BD (191, 201), suggesting that structural connectivity abnormalities may be early features of the disorder.

Recent studies have been performed in unaffected first-degree relatives of individuals with BD to address the important possibility that the white matter abnormalities may be associated with risk for BD (201–205). One study calculated an estimated genetic liability of BD, among subjects with BD, unaffected first degree relatives, and healthy comparison subjects, and demonstrated a negative correlation between the genetic liability of BD and the FA in distributed white matter regions (206). Versace et al. (205) found evidence to support alterations in the developmental trajectory of white matter development in temporal associative tracts as well as corpus callosum in youths at risk for BD, compared to low-risk youths. Another study suggests the white matter differences may underlie risk for mood cycling as an inverse correlation between cyclothymia scales and white matter integrity was observed in unaffected first-degree relatives (204). Moreover, evidence suggests that the distribution of white matter abnormalities might help to distinguish BD from major depressive disorder (207).

Functional connectivity

The functional neuroimaging findings presented above were from studies that used conventional analyses that provided information about the functioning within brain regions. Functional connectivity analyses assess the temporal coupling between activity in different brain regions, which provides a measure of how well the regions are able to coordinate their responses. In adults with BD, these studies have demonstrated abnormalities in the functional connectivity between the amygdala and the VPFC in individuals at rest and during performance of emotional face processing tasks (208–214), and aspects of this dysfunctional connectivity may distinguish BD from major depressive disorder (215). These abnormalities have also been shown in adults with BD across mood states, suggesting that they may be trait features of the disorder. One study has also shown increases in interhemispheric functional connectivity between the left and right VPFC (209) in BD individuals at rest. This is potentially consistent with both theories of abnormalities in right-left hemispheric balance in the disorder from behavioral neurology, as well as the DTI findings of abnormal structural connectivity in the corpus callosum.

Although two prior functional connectivity studies including both pre-adolescent and adolescent youths ages 7 to 17 years with BD did not demonstrate amygdala–anterior paralimbic connectivity abnormalities (210, 212), one study of face processing in youth with BD did show reduced functional connectivity between amygdala and posterior association cortices (212), suggesting that abnormalities in the sensory association cortex input to the amygdala may be an early feature of BD, while amygdala–anterior paralimbic functional connectivity abnormalities may evolve over adolescence or early adulthood. However, longitudinal studies are needed to better characterize the trajectory of these abnormalities in BD through adolescence and beyond.

Structural connectivity–functional connectivity relationships

As in the regional structure-function analysis described above, studies are emerging that combine structural and functional connectivity analyses. In one example, associations between decreases in functional connectivity between the amygdala and the VACC with decreases in the structural integrity of the white matter providing connections between the two structures (214) were observed. This observation suggests the structural and functional connectivity abnormalities are interrelated.

Summary of connectivity findings

Recent structural and functional connectivity studies in BD build on the regional structural and functional studies above, and suggest the importance not only of abnormalities in BD within the nodes of the amygdala–anterior paralimbic neural system, but also of abnormalities in the connections among them. These studies build upon the postmortem literature, which suggests particular glial cell deficits in frontal and mesial temporal regions in BD, strengthening the case for white matter dysfunction as impacting BD symptomatology on the network level. Although this is a relatively new avenue of study, some DTI and functional connectivity studies are already hinting that some connectivity abnormalities may be present early in the course of illness, and may reflect vulnerability to BD, while others may not be fully expressed until adulthood.

Overall summary

Despite the many challenges facing the field of neuroimaging research of BD, including clinical heterogeneity of BD, varying mood states, and medication regimens of the subjects, and differing imaging methodologies across research groups, as well as the small sample sizes that can limit the ability to assess the influence of these heterogeneous factors, there is a remarkable convergence of findings across neuroimaging studies of BD. Consistent with predictions of early behavioral neurology models, an amygdala–anterior paralimbic neural system appears to have a central role in the disorder. Findings in the amygdala and in the VPFC, as well as in their connections, have been particularly consistent results, with abnormalities reported across mood states of the disorder and in studies employing many different experimental paradigms suggesting that dysfunction in these regions is a trait feature of the disorder. There also seems to be a dynamic, state-related component to VPFC dysfunction within BD, with mania associated with largely right-sided dysfunction, and depression with largely left-sided dysfunction, during functional neuroimaging of emotional task performance.

Abnormalities in subcortical components of the system, and potentially OPC, as well as connections between these regions, appear to be early features of the disorder, whereas abnormalities in more rostral PFC may continue to evolve during late adolescence and early adulthood. These findings are supportive of a view of BD as a neurodevelopmental disorder, albeit further longitudinal studies are critically needed. Increasingly, genetic factors that may influence the development of the disorder are being identified, and studies that integrate genetics and neuroimaging methods are being performed (104, 105, 138, 216–218); these may also help to elucidate the mechanisms that underlie the development of the disorder. These studies may also help in understanding heterogeneity in the disorder, for example, by identifying biologically separable subtypes within BD. Finally, loss of white matter integrity, both at the cellular level (as seen in reductions in glial counts in postmortem studies) and at the network level (based on white matter connectivity studies), appears to be a key element of BD pathophysiology that may contribute to abnormalities in functional connectivity disturbances within the system. The mechanism by which white matter integrity is damaged is not completely understood and is a promising avenue for future research.

Limitations to current methods include resolution of imaging techniques, with difficulty imaging structures, such as the hypothalamus, that may be important in BD. Activation paradigms employed to date have targeted limited subsets of the implicated regions. While the inclusion of medicated subjects in many studies has made interpretation of the research more challenging, requiring consideration of the degree to which medications may have confounded or diminished differences between BD and healthy groups, this work has also provided preliminary evidence that pharmacotherapy may have salutary effects on some of

the structural and functional dysfunction implicated in BD. Similarly, studies that take into account genetic variation between BD patients, while making interpretation more complex, have opened up avenues into investigating gene-by-illness effects on the structure and function of key regions. Initial studies have tended to have smaller sample sizes and to measure less variables over less time. Larger sample sizes will improve the signal to noise ratio in studies, and as more variables are recognized and carefully measured, a more refined view of BD, as well as its interaction with various clinical factors such as medication and use of illicit substances, and how these impact different regions of the brain will emerge. Longitudinal studies will be important in examining the neurodevelopmental aspects of BD that have been suggested.

As research findings from the various imaging modalities continue to accrue, a more comprehensive picture of the neural system involved in BD will continue to be clarified. A greater understanding of the involvement of the nodes within this system, and their interconnections, may inform new methods for diagnosis and monitoring. Further investigation of what may be separable BD subtypes, such as adolescent onset BD, or BD associated with certain genotypes, may aid the development of more targeted treatments. Further research on neurodevelopment in the disorder may elucidate pathophysiology and guide future research towards new opportunities for the early identification, treatment, and someday prevention of this disabling disorder.

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References

1. Amaral DG, Price JL. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J Comp Neurol*. 1984; 230:465–496. [PubMed: 6520247]
2. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995; 118:279–306. [PubMed: 7895011]
3. Mesulam MM, Mufson EJ. Insula of the old world monkey. I. Architectonics in the insuloorbito-temporal component of the paralimbic brain. *J Comp Neurol*. 1982; 212:1–22. [PubMed: 7174905]
4. 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. [PubMed: 1460107]
5. Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR. Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *J Comp Neurol*. 1995; 359:490–506. [PubMed: 7499543]
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. [PubMed: 10377356]
7. Blumer, D.; Benson, DF. *Psychiatric aspects of neurologic disease*. New York: Grune and Stratton; 1975.
8. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. *Am J Psychiatry*. 1984; 141:1084–1087. [PubMed: 6465386]
9. Cummings, JL. *Clinical neuropsychiatry*. Orlando: Grune and Stratton; 1986.
10. Damasio, AR.; Anderson, SW. The Frontal Lobes. In: Heilman, KM.; Valenstein, E., editors. *Clinical Neuropsychology*. third. Oxford: Oxford University Press; 1993.
11. 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. [PubMed: 8178168]

12. Jastrowitz M. Beitrage zur localisation im grosshirn and uber deren praktische verwerthung. Dtsch Med Wochenshr. 1888; 14:81–83.
13. Oppenheim H. Zur pathologie der grosshirngeschwulste. Arch Psychiatry. 1889; 21:560–578.
14. 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. [PubMed: 7798983]
15. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci. 1996; 351:1413–1420. [PubMed: 8941953]
16. Schoenbaum G, Chiba AA, Gallagher M. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci. 1998; 1:155–159. [PubMed: 10195132]
17. Nauta WJ. The problem of the frontal lobe: a reinterpretation. J Psychiatr Res. 1971; 8:167–187. [PubMed: 5000109]
18. Rolls, ET. The Brain and Emotion. Oxford: Oxford University Press; 1999.
19. Addington J, Addington D. Facial affect recognition and information processing in schizophrenia and bipolar disorder. Schizophr Res. 1998; 32:171–181. [PubMed: 9720122]
20. Lembke A, Ketter TA. Impaired recognition of facial emotion in mania. Am J Psychiatry. 2002; 159:302–304. [PubMed: 11823275]
21. McClure EB, Pope K, Hoberman AJ, Pine DS, Leibenluft E. Facial expression recognition in adolescents with mood and anxiety disorders. Am J Psychiatry. 2003; 160:1172–1174. [PubMed: 12777278]
22. Rich BA, Grimley ME, Schmajuk M, Blair KS, Blair RJ, Leibenluft E. Face emotion labeling deficits in children with bipolar disorder and severe mood dysregulation. Dev Psychopathol. 2008; 20:529–546. [PubMed: 18423093]
23. Schenkel LS, Pavuluri MN, Herbener ES, Harral EM, Sweeney JA. Facial emotion processing in acutely ill and euthymic patients with pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2007; 46:1070–1079. [PubMed: 17667485]
24. Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. Nature. 1998; 393:470–474. [PubMed: 9624002]
25. 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.
26. Starkstein SE, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry. 1991; 29:149–158. [PubMed: 1995084]
27. Wexler BE. Cerebral laterality and psychiatry: a review of the literature. Am J Psychiatry. 1980; 137:279–291. [PubMed: 6986798]
28. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. Arch Neurol. 1977; 34:454–467. [PubMed: 889477]
29. Flor-Henry P. Schizophrenic-like reactions and affective psychoses associated with temporal lobe epilepsy: etiological factors. Am J Psychiatry. 1969; 126:400–404. [PubMed: 5801258]
30. Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitisation in the longitudinal course of affective illness. Br J Psychiatry. 1986; 149:191–201. [PubMed: 3535979]
31. 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. Psychopharmacol. 2005; 183:308–313.
32. Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. J Neuropsychiatry Clin Neurosci. 1994; 6:358–370. [PubMed: 7841807]
33. Lauterbach EC. Bipolar disorders, dystonia, and compulsion after dysfunction of the cerebellum, dentatorubrothalamic tract, and substantia nigra. Biol Psychiatry. 1996; 40:726–730. [PubMed: 8894064]
34. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. Ann Neurol. 1990; 28:57–64. [PubMed: 2375634]

35. Mayberg HS, Starkstein SE, Peyser CE, Brandt J, Dannals RF, Folstein SE. Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease. *Neurology*. 1992; 42:1791–1797. [PubMed: 1387463]
36. Mayberg HS. Frontal lobe dysfunction in secondary depression. *J Neuropsychiatry Clin Neurosci*. 1994; 6:428–442. [PubMed: 7841814]
37. Starr, MA. Organic nervous diseases. New York: Lea Brothers & Co.; 1903.
38. Moniz E. Prefrontal leucotomy in the treatment of mental disorders. 1937. *Am J Psychiatry*. 1994; 151:236–239. [PubMed: 8192205]
39. Green EK, Raybould R, Macgregor S, et al. Operation of the schizophrenia susceptibility gene, neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder. *Arch Gen Psychiatry*. 2005; 62:642–648. [PubMed: 15939841]
40. Kim S, Webster MJ. Correlation analysis between genome-wide expression profiles and cytoarchitectural abnormalities in the prefrontal cortex of psychiatric disorders. *Mol Psychiatry*. 2010; 15:326–336. [PubMed: 18762803]
41. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA*. 1998; 95:13290–13295. [PubMed: 9789081]
42. Rajkowska G. Cell pathology in mood disorders. *Semin Clin Neuropsychiatry*. 2002; 7:281–292. [PubMed: 12382210]
43. Tkachev D, Mimmack ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet*. 2003; 362:798–805. [PubMed: 13678875]
44. 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. [PubMed: 14984887]
45. 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. [PubMed: 17566708]
46. Machado CJ, Bachevalier J. Non-human primate models of childhood psychopathology: the promise and the limitations. *J Child Psychol Psychiatry*. 2003; 44:64–87. [PubMed: 12553413]
47. Schumann CM, Bauman MD, Amaral DG. Abnormal structure or function of the amygdala is a common component of neurodevelopmental disorders. *Neuropsychologia*. 2011; 49:745–759. [PubMed: 20950634]
48. Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*. 1994; 372:669–672. [PubMed: 7990957]
49. Shaw P, Lawrence EJ, Radbourne C, Bramham J, Polkey CE, David AS. The impact of early and late damage to the human amygdala on 'theory of mind' reasoning. *Brain*. 2004; 127:1535–1548. [PubMed: 15155523]
50. Hamann SB, Adolphs R. Normal recognition of emotional similarity between facial expressions following bilateral amygdala damage. *Neuropsychologia*. 1999; 37:1135–1141. [PubMed: 10509835]
51. Liao D, Scannevin RH, Haganir R. Activation of silent synapses by rapid activity-dependent synaptic recruitment of AMPA receptors. *J Neurosci*. 2001; 21:6008–6017. [PubMed: 11487624]
52. Maletic-Savatic M, Malinow R, Svoboda K. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science*. 1999; 283:1923–1927. [PubMed: 10082466]
53. Spitzer NC. Electrical activity in early neuronal development. *Nature*. 2006; 444:707–712. [PubMed: 17151658]
54. Bertolino A, Saunders RC, Mattay VS, Bachevalier J, Frank JA, Weinberger DR. Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporo-limbic lesions: a proton magnetic resonance spectroscopic imaging study. *Cereb Cortex*. 1997; 7:740–748. [PubMed: 9408038]
55. Saunders RC, Kolachana BS, Bachevalier J, Weinberger DR. Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. *Nature*. 1998; 393:169–171. [PubMed: 9603519]

56. Heinz A, Saunders RC, Kolachana BS, et al. Striatal dopamine receptors and transporters in monkeys with neonatal temporal limbic damage. *Synapse*. 1999; 32:71–79. [PubMed: 10231127]
57. Bunney WE Jr, Goodwin FK, Murphy DL, House KM, Gordon EK. The “switch process” in manic-depressive illness. II. Relationship to catecholamines, REM sleep, and drugs. *Arch Gen Psychiatry*. 1972; 27:304–309. [PubMed: 4340658]
58. Flor-Henry P. Lateralized temporal-limbic dysfunction and psychopathology. *Ann NY Acad Sci*. 1976; 280:777–797. [PubMed: 797292]
59. 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. [PubMed: 9672058]
60. 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. [PubMed: 14662552]
61. Pearson 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. [PubMed: 8988790]
62. Strakowski SM, DelBello MP, Sax KW, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch Gen Psychiatry*. 1999; 56:254–260. [PubMed: 10078503]
63. 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. [PubMed: 15908839]
64. 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. [PubMed: 15364037]
65. 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. [PubMed: 14996140]
66. Dickstein DP, Milham MP, Nugent AC, et al. Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. *Arch Gen Psychiatry*. 2005; 62:734–741. [PubMed: 15997014]
67. Rosso IM, Killgore WD, Cintron CM, Gruber SA, Tohen M, Yurgelun-Todd DA. Reduced amygdala volumes in first-episode bipolar disorder and correlation with cerebral white matter. *Biol Psychiatry*. 2007; 61:743–749. [PubMed: 17123471]
68. 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. [PubMed: 15246455]
69. Bitter SM, Mills NP, Adler CM, Strakowski SM, DelBello MP. Progression of amygdala volumetric abnormalities in adolescents after their first manic episode. *J Am Acad Child Adolesc Psychiatry*. 2011; 50:1017–1026. [PubMed: 21961776]
70. Bowley MP, Drevets WC, Ongur D, Price JL. Low glial numbers in the amygdala in major depressive disorder. *Biol Psychiatry*. 2002; 52:404–412. [PubMed: 12242056]
71. 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. [PubMed: 18185112]
72. Scherk H, Gruber O, Menzel P, et al. 5-HTTLPR genotype influences amygdala volume. *Eur Arch Psychiatry Clin Neurosci*. 2009; 259:212–217. [PubMed: 19224115]
73. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007; 87:873–904. [PubMed: 17615391]
74. Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–827. [PubMed: 9126739]
75. 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. [PubMed: 17027928]
76. 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. [PubMed: 16414030]

77. 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. [PubMed: 15033185]
78. Foland-Ross LC, Thompson PM, Sugar CA, et al. Investigation of cortical thickness abnormalities in lithium-free adults with bipolar I disorder using cortical pattern matching. *Am J Psychiatry.* 2011; 168:530–539. [PubMed: 21285139]
79. 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. [PubMed: 18207705]
80. 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. [PubMed: 16403181]
81. 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. [PubMed: 19402934]
82. 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. [PubMed: 16135622]
83. 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. [PubMed: 12114000]
84. Lyoo IK, Kim MJ, Stoll AL, et al. Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry.* 2004; 55:648–651. [PubMed: 15013835]
85. Lyoo IK, Sung YH, Dager SR, et al. Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disord.* 2006; 8:65–74. [PubMed: 16411982]
86. 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. [PubMed: 17276600]
87. 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. [PubMed: 16256376]
88. Baloch HA, Hatch JP, Olvera RL, et al. Morphology of the subgenual prefrontal cortex in pediatric bipolar disorder. *J Psychiatr Res.* 2010; 44:1106–1110. [PubMed: 20488457]
89. 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. [PubMed: 15708300]
90. Raznahan A, Lerch JP, Lee N, et al. Patterns of coordinated anatomical change in human cortical development: a longitudinal neuroimaging study of maturational coupling. *Neuron.* 2011; 72:873–884. [PubMed: 22153381]
91. Wang F, Kalmar JH, Womer FY, et al. Olfactocentric paralimbic cortex morphology in adolescents with bipolar disorder. *Brain.* 2011; 134:2005–2012. [PubMed: 21666263]
92. Gogtay N, Odonez A, Herman DH, et al. Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *J Child Psychol Psychiatry.* 2007; 48:852–862. [PubMed: 17714370]
93. Blumberg HP, Kaufman J, Martin A, Charney DS, Krystal JH, Peterson BS. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. *Ann NY Acad Sci.* 2004; 1021:376–383. [PubMed: 15251913]
94. Stanfield AC, Moorhead TWJ, Job DE, et al. Structural abnormalities of ventrolateral and orbitofrontal cortex in patients with familial bipolar disorder. *Bipolar Disord.* 2009; 11:135–144. [PubMed: 19267696]
95. 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. [PubMed: 10903411]
96. 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. [PubMed: 18356767]

97. 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. [PubMed: 15994707]
98. Hauser P, Matochik J, Altshuler LL, et al. 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. [PubMed: 10940444]
99. 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. [PubMed: 9766770]
100. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet*. 2000; 356:1241–1242. [PubMed: 11072948]
101. Noga JT, Vldar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. *Psychiatry Res*. 2001; 106:25–34. [PubMed: 11231097]
102. Swayze VW 2nd, 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. [PubMed: 1547297]
103. 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. [PubMed: 10025437]
104. Chepenik LG, Fredericks C, Papademetris X, et al. Effects of the brain-derived neurotrophic growth factor val66met variation on hippocampus morphology in bipolar disorder. *Neuropsychopharmacol*. 2009; 34:944–951.
105. 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. [PubMed: 17895927]
106. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry*. 2006; 59:1116–1127. [PubMed: 16631126]
107. Geller B, Williams M, Zimmerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord*. 1998; 51:81–91. [PubMed: 10743841]
108. Muller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. *Br J Psychiatry*. 2006; 189:317–323. [PubMed: 17012654]
109. Hwang J, Lyoo IK, Dager SR, et al. Basal ganglia shape alterations in bipolar disorder. *Am J Psychiatry*. 2006; 163:276–285. [PubMed: 16449482]
110. 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. [PubMed: 12071513]
111. Anand BK, Malhotra CL, Singh B, Dua S. Cerebellar projections to limbic system. *J Neurophysiol*. 1959; 22:451–457. [PubMed: 13673296]
112. Heath RG, Dempsey CW, Fontana CJ, Myers WA. Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats. *Biol Psychiatry*. 1978; 13:501–529. [PubMed: 728506]
113. Ramnani N. The primate cortico-cerebellar system: anatomy and function. *Nat Rev Neurosci*. 2006; 7:511–522. [PubMed: 16791141]
114. Snider RS, Maiti A. Cerebellar contributions to the Papez circuit. *J Neurosci Res*. 1976; 2:133–146. [PubMed: 950678]
115. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*. 1998; 121:561–579. [PubMed: 9577385]
116. Supple WF Jr, Leaton RN, Fanselow MS. Effects of cerebellar vermal lesions on species-specific fear responses, neophobia, and taste-aversion learning in rats. *Physiol Behav*. 1987; 39:579–586. [PubMed: 3588702]
117. Supple WF Jr, Cranney J, Leaton RN. Effects of lesions of the cerebellar vermis on VMH lesion-induced hyperdefensiveness, spontaneous mouse killing, and freezing in rats. *Physiol Behav*. 1988; 42:145–153. [PubMed: 3368533]

118. Tavano A, Grasso R, Gagliardi C, et al. Disorders of cognitive and affective development in cerebellar malformations. *Brain*. 2007; 130:2646–2660. [PubMed: 17872929]
119. Yadalam KG, Jain AK, Simpson GM. Mania in two sisters with similar cerebellar disturbance. *Am J Psychiatry*. 1985; 142:1067–1069. [PubMed: 4025624]
120. DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. *Neuropsychopharmacol*. 1999; 21:63–68.
121. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am J Psychiatry*. 2005; 162:1530–1532. [PubMed: 16055777]
122. 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. [PubMed: 18272276]
123. 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. [PubMed: 11684138]
124. Womer FY, Wang F, Chepenik LG, et al. Sexually dimorphic features of vermis morphology in bipolar disorder. *Bipolar Disord*. 2009; 11:753–758. [PubMed: 19839998]
125. Almeida JR, Versace A, Hassel S, Kupfer DJ, Phillips ML. Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. *Biol Psychiatry*. 2010; 67:414–421. [PubMed: 19931855]
126. 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. [PubMed: 15930074]
127. 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. [PubMed: 18402630]
128. 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. [PubMed: 11830178]
129. 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. [PubMed: 18310580]
130. 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. [PubMed: 19454919]
131. 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. [PubMed: 11164756]
132. 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. [PubMed: 15013826]
133. Mah L, Zarate CA Jr, Singh J, et al. Regional cerebral glucose metabolic abnormalities in bipolar II depression. *Biol Psychiatry*. 2007; 61:765–775. [PubMed: 17027930]
134. 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. [PubMed: 14984424]
135. 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. [PubMed: 17097071]
136. 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 USA*. 2006; 103:8900–8905. [PubMed: 16735472]
137. Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WDS, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord*. 2000; 2:237–248. [PubMed: 11249801]
138. 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. *Neuropsychopharmacol*. 2009; 34:1301–1310.

139. Foland-Ross LC, Bookheimer SY, Lieberman MD, et al. Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. *Neuroimage*. 2012; 59:738–744. [PubMed: 21854858]
140. 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. *Neuropharmacol*. 2002; 42:522–529.
141. 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):S71–80. [PubMed: 11986998]
142. Tian LM, Alkadhi KA. Valproic acid inhibits the depolarizing rectification in neurons of rat amygdala. *Neuropharmacol*. 1994; 33:1131–1138.
143. Berretta S, Pantazopoulos H, Lange N. Neuron numbers and volume of the amygdala in subjects diagnosed with bipolar disorder or schizophrenia. *Biol Psychiatry*. 2007; 62:884–893. [PubMed: 17698040]
144. Pantazopoulos H, Lange N, Baldessarini RJ, Berretta S. Parvalbumin neurons in the entorhinal cortex of subjects diagnosed with bipolar disorder or schizophrenia. *Biol Psychiatry*. 2007; 61:640–652. [PubMed: 16950219]
145. Wang AY, Lohmann KM, Yang CK, et al. Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathol*. 2011; 122:615–626. [PubMed: 21968533]
146. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry*. 2004; 9:609–620. [PubMed: 14708030]
147. Konradi C, Zimmerman EI, Yang CK, et al. Hippocampal interneurons in bipolar disorder. *Arch Gen Psychiatry*. 2011; 68:340–350. [PubMed: 21135314]
148. Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biol Psychiatry*. 2005; 57:252–260. [PubMed: 15691526]
149. McIntosh AM, Whalley HC, McKirdy J, et al. Prefrontal function and activation in bipolar disorder and schizophrenia. *Am J Psychiatry*. 2008; 165:378–384. [PubMed: 18198268]
150. 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. [PubMed: 16310510]
151. 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. [PubMed: 10588416]
152. 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. [PubMed: 12796223]
153. 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. [PubMed: 15184035]
154. Rubinsztein JS, Fletcher PC, Rogers RD, et al. Decision-making in mania: a PET study. *Brain*. 2001; 124:2550–2563. [PubMed: 11701607]
155. Strakowski SM, Eliassen JC, Lamy M, et al. Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. *Biol Psychiatry*. 2011; 69:381–388. [PubMed: 21051038]
156. 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. [PubMed: 16112653]
157. Townsend J, Bookheimer SY, Foland-Ross LC, Sugar CA, Altshuler LL. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Res*. 2010; 182:22–29. [PubMed: 20227857]

158. Frangou S, Kington J, Raymont V, Shergill SS. Examining ventral and dorsal prefrontal function in bipolar disorder: a functional magnetic resonance imaging study. *Eur Psychiatry*. 2008; 23:300–308. [PubMed: 17656073]
159. 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. [PubMed: 16411978]
160. 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. [PubMed: 14643095]
161. 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. [PubMed: 16449479]
162. 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. [PubMed: 16225562]
163. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP. A preliminary fMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacol*. 2004; 29:1734–1740.
164. 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. [PubMed: 17202544]
165. 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. [PubMed: 12832254]
166. Kim E, Jung YC, Ku J, et al. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:1409–1416. [PubMed: 19632283]
167. Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2009; 48:308–319. [PubMed: 19242292]
168. Van der Schot A, Kahn R, Ramsey N, Nolen W, Vink M. Trait and state dependent functional impairments in bipolar disorder. *Psychiatry Res*. 2010; 184:135–142. [PubMed: 21050725]
169. Frangou S, Haldane M, Roddy D, Kumari V. Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. *Biol Psychiatry*. 2005; 58:838–839. [PubMed: 16043135]
170. Deckersbach T, Dougherty DD, Savage C, et al. Impaired recruitment of the dorsolateral prefrontal cortex and hippocampus during encoding in bipolar disorder. *Biol Psychiatry*. 2006; 59:138–146. [PubMed: 16169530]
171. Lagopoulos J, Malhi GS. A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. *Neuroreport*. 2007; 18:1583–1587. [PubMed: 17885606]
172. Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R, Ketter T. Is a lack of disgust something to fear? A functional magnetic resonance imaging facial emotion recognition study in euthymic bipolar disorder patients. *Bipolar Disord*. 2007; 9:345–357. [PubMed: 17547581]
173. Blumberg HP, Stern E, Martinez D, et al. Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*. 2000; 48:1045–1052. [PubMed: 11094137]
174. Brooks JO 3rd, Wang PW, Bonner JC. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. *J Psychiatr Res*. 2009; 43:181–188. [PubMed: 18582900]
175. 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. [PubMed: 12928105]
176. 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. [PubMed: 15225144]

177. Chang K, Adleman NE, Dienes K, Simeonova DI, Menon V, Reiss A. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder - A functional magnetic resonance imaging investigation. *Arch Gen Psychiatry*. 2004; 61:781–792. [PubMed: 15289277]
178. Caligiuri MP, Brown GG, Meloy MJ, Eberson S, Niculescu AB, Lohr JB. Striatopallidal regulation of affect in bipolar disorder. *J Affect Disord*. 2006; 91:235–242. [PubMed: 16503055]
179. Marchand WR, Lee JN, Thatcher GW, et al. A functional MRI study of a paced motor activation task to evaluate frontal-subcortical circuit function in bipolar depression. *Psychiatry Res*. 2007; 155:221–230. [PubMed: 17588725]
180. Wessa M, Houenou J, Paillere-Martinot ML, et al. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry*. 2007; 164:638–646. [PubMed: 17403978]
181. 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. [PubMed: 16135630]
182. 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. [PubMed: 11904131]
183. Atmaca M, Ozdemir H, Yildirim H. Corpus callosum areas in first-episode patients with bipolar disorder. *Psychol Med*. 2007; 37:699–704. [PubMed: 17224093]
184. 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. [PubMed: 14643097]
185. Brambilla P, Nicoletti M, Sassi RB, et al. Corpus callosum signal intensity in patients with bipolar and unipolar disorder. *J Neurol Neurosurg Psychiatry*. 2004; 75:221–225. [PubMed: 14742592]
186. Caetano SC, Silveira CM, Kaur S, et al. Abnormal corpus callosum myelination in pediatric bipolar patients. *J Affect Disord*. 2008; 108:297–301. [PubMed: 18037496]
187. 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. [PubMed: 2354225]
188. 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. [PubMed: 15820230]
189. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*. 2002; 15:435–455. [PubMed: 12489094]
190. Adler CM, Holland SK, Schmithorst V, et al. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disord*. 2004; 6:197–203. [PubMed: 15117398]
191. 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. [PubMed: 16449490]
192. Beyer JL, Taylor WD, MacFall JR, et al. Cortical white matter microstructural abnormalities in bipolar disorder. *Neuropsychopharmacol*. 2005; 30:2225–2229.
193. 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. [PubMed: 18452442]
194. 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. [PubMed: 17471288]
195. 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. [PubMed: 16542190]
196. 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. [PubMed: 18762590]

197. 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. [PubMed: 18669996]
198. Zanetti MV, Jackowski MP, Versace A, et al. State-dependent microstructural white matter changes in bipolar I depression. *Eur Arch Psychiatry Clin Neurosci*. 2009; 259:316–328. [PubMed: 19255710]
199. 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. [PubMed: 18620337]
200. Yurgelun-Todd DA, Silveri MM, Gruber SA, Rohan ML, Pimentel PJ. White matter abnormalities observed in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disord*. 2007; 9:504–512. [PubMed: 17680921]
201. Frazier JA, Breeze JL, Papadimitriou G, et al. White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disord*. 2007; 9:799–809. [PubMed: 18076529]
202. Kieseppa T, van Erp TG, Haukka J, et al. Reduced left hemispheric white matter volume in twins with bipolar I disorder. *Biol Psychiatry*. 2003; 54:896–905. [PubMed: 14573317]
203. McDonald C, Bullmore ET, Sham PC, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry*. 2004; 61:974–984. [PubMed: 15466670]
204. Sprooten E, Sussmann JE, Clugston A, et al. White matter integrity in individuals at high genetic risk of bipolar disorder. *Biol Psychiatry*. 2011; 70:350–356. [PubMed: 21429475]
205. Versace A, Ladouceur CD, Romero S, et al. Altered development of white matter in youth at high familial risk for bipolar disorder: a diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry*. 2010; 49:1249–1259. [PubMed: 21093774]
206. Chaddock CA, Barker GJ, Marshall N, et al. White matter microstructural impairments and genetic liability to familial bipolar I disorder. *Br J Psychiatry*. 2009; 194:527–534. [PubMed: 19478293]
207. Versace A, Almeida JR, Quevedo K, et al. Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. *Biol Psychiatry*. 2010; 68:560–567. [PubMed: 20598288]
208. Anand A, Li Y, Wang Y, Lowe MJ, Dzemidzic M. Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Res*. 2009; 171:189–198. [PubMed: 19230623]
209. Chepenik LG, Raffo M, Hampson M, et al. Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Res*. 2010; 182:207–210. [PubMed: 20493671]
210. Dickstein DP, Gorrostieta C, Ombao H, et al. Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. *Biol Psychiatry*. 2010; 68:839–846. [PubMed: 20739018]
211. Foland LC, Altshuler LL, Bookheimer SY, Eisenberger N, Townsend J, Thompson PM. Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. *Psychiatry Res*. 2008; 162:27–37. [PubMed: 18063349]
212. Rich BA, Fromm SJ, Berghorst LH, et al. Neural connectivity in children with bipolar disorder: impairment in the face emotion processing circuit. *J Child Psychol Psychiatry*. 2008; 49:88–96. [PubMed: 18181882]
213. Versace A, Thompson WK, Zhou D, et al. Abnormal left and right amygdala–orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. *Biol Psychiatry*. 2010; 67:422–431. [PubMed: 20159144]
214. 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. [PubMed: 19427632]
215. Almeida JR, Versace A, Mechelli A, et al. Abnormal amygdala–prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry*. 2009; 66:451–459. [PubMed: 19450794]

216. Blumberg HP, Wang F, Chepenik LG, et al. Influence of vascular endothelial growth factor variation on human hippocampus morphology. *Biol Psychiatry*. 2008; 64:901–903. [PubMed: 18707678]
217. McIntosh AM, Moorhead TW, Job D, et al. The effects of a neuregulin 1 variant on white matter density and integrity. *Mol Psychiatry*. 2008; 13:1054–1059. [PubMed: 17925794]
218. Wang F, McIntosh AM, He Y, Gelernter J, Blumberg HP. The association of genetic variation in CACNA1C with structure and function of a frontotemporal system. *Bipolar Disord*. 2011; 13:696–700. [PubMed: 22085483]