# Biological Evidence for a Neurodevelopmental Model of Pediatric Bipolar Disorder

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## ABSTRACT

Bipolar disorder (BD) is a chronic illness with high morbidity and mortality. Pediatric onset BD has a more severe course of illness with higher rates of relapse and psychosocial impairment. Discovering interventions early in the course of BD in youth is paramount to preventing full illness expression and improve functioning in these individuals throughout the lifespan. It is therefore important to understand the mechanisms involved in the development of BD in order to determine which youth are at most risk and provide biological targets for early intervention. To serve this cause, we propose a neurodevelopmental model of BD, based on the existing data that implicate prefrontal – subcortical network dysfunction, caused by pre-existing genetic susceptibility and triggered by pathological reactions to stress and chronic inflammatory processes.

## INTRODUCTION

Bipolar disorder (BD) is a chronic, debilitating illness with a lifetime worldwide prevalence of 4.8% and more disability-adjusted life-years lost than major neurological conditions or cancer (1). Pediatric onset BD (PBD) may predict a more severe course of illness (2-8) with high relapse, recurrence, psychosocial impairment, substance use, and suicide at twice the rate of attempted suicides when compared to individuals with unipolar depression (9). Given the high morbidity and mortality associated with PBD, it is important to identify the mechanisms that lead to PBD in order to design better interventions (10), as there is a 10% less likelihood of recovery each year treatment is delayed (11). Despite the adverse impact of this illness, the field has not yet clearly elucidated the developmental pathophysiology of BD (12).

Nonetheless, advances in neuroimaging have allowed researchers to begin to formulate how BD begins and develops in children. Neurobiological studies demonstrate that BD is a brain-based disorder (13, 14). There are therefore brain structural, functional, and chemical changes that occur during the development and course of the disorder. Studies using different types of Magnetic Resonance Imaging (MRI) have found abnormal brain structure, function, and neurochemistry in BD patients. Results from these studies, as well as from other biological studies of BD youth, have begun to allow us to formulate theoretical models of BD development in children and adolescents.

### A PROPOSED NEUROBIOLOGICAL MODEL FOR THE DEVELOPMENT OF BD IN YOUTH

In this paper, we will integrate selected findings from MRI studies in youth with and at-risk for BD, as well as data from adult BD studies, with genetic and other biologic findings to generate a neurobiological model of BD development in youth. The model in brief is such: Children with family histories of BD and mood disorders inherit various genes that create varying levels of risk for BD. These genes translate to neural circuitry and structure that support abnormal mood regulation. Early in life this is detectable as aberrant circuitry between the prefrontal cortex (PFC) and subcortical limbic structures responsible for emotional processing (prefrontal-subcortical circuits). These disruptions

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are detectable as white matter and functional connectivity abnormalities, leading to failure of efficient prefrontal regulation over subcortical structures, and thus gradually increasing mood dysregulation. Over childhood and through puberty into adolescence, these abnormal circuits become reinforced and strengthened through increased environmental stress and maladaptive responses to stress that thereby further create environmental stress in a cyclical fashion. Maladaptive stress reactions may be measured by heightened pro-inflammatory cytokines, which may lead to further neurodevelopmental abnormalities. Once this abnormal circuitry is well-established, anatomic markers may eventually arise that may be unique to children with BD, such as decreased amygdalar volume (15) and these abnormalities may create further vulnerabilities in other brain areas involved with emotional regulation, such as the ventrolateral PFC (VLPFC), the anterior cingulate cortex (ACC), thalamus, striatum, hippocampus, and the cerebellar vermis (16-23). Abnormal reciprocal connections between the dorsolateral PFC (DLPFC) and the amygdala may further be the source of emotional regulation and cognitive difficulties (21, 24-26). Eventually, with repeated mood episodes, prefrontal structures undergo glial and neuronal cell loss, further denigrating the ability of the PFC to regulate mood. This condition leads to rapid cycling and treatment resistance and less stress needed for the next mood episode, consistent with the kindling theory of mood disorders (27). In this paper, we will present the relevant biological findings that provide the basis for this proposed neurodevelopmental model of PBD.

## STRUCTURAL MAGNETIC RESONANCE IMAGING (MRI) FINDINGS

Structural MRI studies in adults and youth with BD have primarily focused on volumetric analyses of whole brain, individual lobes, PFC, striatum, amygdala, hippocampus, and thalamus.

Studies of overall brain volume in youth with BD are inconsistent in their findings, but at least two studies have found decreased overall brain volume in patients with PBD when compared to healthy controls (HC) (24, 28), suggesting reductions in total cerebral volumes that may indicate increased early apoptotic pruning (28). Lobar structural MRI studies also support this idea, as parietal and temporal reductions in areas responsible for attention, facial recognition, and memory have been found (22). The superior temporal gyrus (STG) in the temporal lobe appeared particularly sensitive to volumetric reductions in PBD youth when compared to HC (29). Such structural MRI studies of lobar volumes provide evidence of cortical morphometric abnormalities already present in youth with BD.

Given the high importance of the prefrontal cortex (PFC) in emotional regulation, many structural MRI studies have focused on this area. Relevant areas of the PFC that are involved with emotion regulation, attention, executive functioning, and reward processing and motivation include the DLPFC, VLPFC, ACC and subgenual ACC (sgACC), and ventral prefrontal cortex (VPFC). Decreased DLPFC (30) and VLPFC (31) volumes have been found in PBD subjects, with VLPFC volume inversely correlated with increasing age in PBD (31). Three studies have also shown decreased ACC volumes in BD youth (32-34). One study measured volumetric changes in nine youth before and after developing fully syndromal BD and found bilateral ACC and sgACC volume reductions *after* illness onset (35). Kalmar et al. also found reduced volume in a region encompassing the VPFC to the ACC in a small longitudinal study of youth with BD ages 10-21 scanned two years apart (36). Volumetric findings of the VPFC may also be gender specific, as Najt et al. found enlargement of the VPFC in females with PBD, while males showed VPFC volumetric reductions (37). These volume reductions may be reversible, however, as volume increases are seen in the PFC longitudinally when adults with BD are treated with lithium over time (38). Furthermore, youth with BD who were exposed to mood stabilizers had larger sgACC volumes than those who were not (39). Thus, PFC regions appear to be impacted in PBD, with regional volume loss after the onset of BD, and likely continuing to become more apparent in adulthood, after sustained illness (40), with potential reversal of volume loss due to mood stabilizer treatment.

Other studies have focused on the striatal structures, primarily the caudate, putamen, and nucleus accumbens. These structures are involved in movement, habit-formation, impulse control, reward processing, and decision-making and are central in prefrontal-striatal-subcortical circuits governing these functions. Caudate and putamen findings in PBD have been inconsistent, with some studies showing enlargement (24, 34), and others showing no differences (41), or a possible inverse relationship to age (42). Enlargement of these structures may be due to neuronal proliferation, aberrant synaptic

pruning, or a compensatory neuronal response to some putative toxic event. Data on the nucleus accumbens is inconsistent with regards to increases or decreases in size in PBD over HC. Trends for increased volumes have been found in prepubertal youth with BD, but not postpubertal youth with BD when compared with HC (43). These data, however, may be confounded by the fact that decreased striatal volumes are also found in youth with attention-deficit/hyperactivity disorder (ADHD), which is a common comorbidity in PBD (44). A more recent study examined youth with BD, youth with BD and comorbid ADHD, and HC. Youth with BD and comorbid ADHD had moderately increased nucleus accumbens volumes when compared to HC. Youth with ADHD had decreased putamen and caudate volumes compared to the other groups. No difference was found between youth with BD with comorbid ADHD or without (45). Another recent study showed increased caudate volumes in youth with BD and no ADHD compared to youth with both BD and ADHD. Youth with ADHD in this study also had decreased caudate, putamen, and globus pallidus volumes compared with both HC and BD groups (46). Thus, while the striatum appears to be a key factor in the neuropathophysiology of BD, the nature of involvement may differ depending on the presence or absence of comorbid ADHD symptoms.

The amygdala is responsible for emotional valence and perception, learning, and memory and thus has been extensively studied in PBD (47). Most studies in youth with BD have found decreased amygdalar volumes (22, 24, 30, 34, 41, 48, 49), the most replicated neuroanatomical finding in PBD. Bitter et al. found that during their first manic episode, adolescents with newly diagnosed PBD had no difference in amygdalar volumes when compared to HC or to adolescents with ADHD only. However, one year later, the adolescents with BD showed significantly less growth in amygdalar volume when compared to either HC or the ADHD group (50). These findings suggest that amygdalar volumes in youth with BD may only be found abnormally low after the onset of mania, and is therefore likely a sequela of BD rather than a cause. In support of this theory are studies in adults with BD, which often have found increased amygdalar volume compared with HC (15, 51, 52), which may be due to exposure to medications such as lithium (53) or due to other mechanisms caused by repeated mood episodes or exogenous factors other than medications. Additionally, a greater number of life events has been found to be associated with decreased amygdala as well as nucleus accumbens volumes in youth with BD (54). If such stressful events do contribute to smaller amygdalar volume, it is less likely that repeated mood episodes are at the root of enlarged volumes in adults. Nonetheless, it is possible that the amygdala and other subcortical structures are morphometrically responsive in a differential manner to environmental factors such as life stress and psychotropic medications versus endogenous factors, such as mood episodes.

Hippocampal volumetric findings are less consistent. The hippocampus is involved with stress regulation, memory, spatial coding, appraisal, and emotional responses via inhibitory pathways to other subcortical structures. Two studies have shown reductions in hippocampal volume (22, 55) when comparing youth with BD to HC, but two other studies have shown no difference (24, 41). A recent study examining a familial BD sample showed hippocampal volume was inversely correlated to anxiety scores (56), suggesting that heterogeneity of sample for lifetime stress exposure and degrees of pathologic reaction to stress may account for the mixed hippocampal findings in the literature. Nevertheless, the hippocampus remains a structure sensitive to morphometric changes under stress. Given the known cognitive deficits found in BD, it will be important to further study the impact of exogenous factors on this structure.

The thalamus relays information to different brain areas and regulates states of sleep, wakefulness, and arousal. However, no published studies have found volumetric differences in the thalamus in PBD relative to HC (22, 24, 41, 57). Lastly, several other areas of the brain that have volumetric differences in adults with BD when compared to HC but not in PBD include the corpus callosum (58) and the pituitary gland (59). The cerebellar vermis has also had increasingly more focus as a structure involved with emotion regulation, but to date only trend level reductions have been found in youth with BD (23).

As the above studies were conducted in youth with fully syndromal BD, the question arises as to whether these findings are an underlying cause of BD, or are instead caused by the repeated mood episodes inherent to BD. Many confounding factors exist in these studies, including medication exposure, comorbidities, age at illness onset, or substance use. Additionally, clinical heterogeneity of study population may mean neurobiological heterogeneity, which may "wash out" or obscure underlying biological differences. Thus, examining youth before illness

onset, when ostensibly fewer of these confounding factors exist, and again after illness onset in a longitudinal manner, would be ideal. Researchers have attempted to reduce the impact of these factors by examining child offspring of parents with BD. Such youth are considered at high-risk (HR) for developing BD, particularly those offspring already with mood symptoms (60). In one study of HR youth, Singh et al. found no overall structural abnormalities in a sample of asymptomatic and symptomatic HR youth relative to HC (61), but did find enlargement of the PFC in asymptomatic HR youth compared to symptomatic HR and HC groups. A different study of asymptomatic HR youth found gray matter volume increases in the parahippocampal gyri (62), suggesting either BD trait related structural changes that predate onset of symptomatic illness or a marker of resilience to mood disorder development given that these offspring were healthy. The finding of decreased amygdalar volumes found in PBD also has not been reported in at-risk samples (61-63) or in first episode mania samples. Karchemskiy et al. studied symptomatic at-risk offspring of parents with BD, theoretically closer to BD onset than healthy offspring, and found no significant volumetric differences in the amygdala, hippocampus, and thalamus (63). These findings suggest that volumetric reduction of these subcortical structures is likely a consequence of the bipolar disease process rather than an etiological finding or risk factor.

Taken together, these studies indicate structural abnormalities in relevant PFC and subcortical regions in youth with BD. Longitudinal studies are needed to determine whether these volumetric findings are indeed risk factors or consequences of BD, but HR studies so far support that these morphometric abnormalities are indeed consequences. Such longitudinal studies thus far have found ACC volume loss (64) and persistently decreased amygdalar volume in adolescents with BD over time (48). Further studies such as these and in larger sample sizes are needed to address developmental factors that may influence results from cross-sectional neuroimaging studies.

## WHITE MATTER AND DIFFUSION TENSOR IMAGING (DTI)

Converging evidence suggests white matter (WM) alterations are involved in the pathophysiology of BD (65). WM hyperintensities seen on T2 MRI images are the most consistent finding in BD and have been reported in adults and children with BD (65) as well as in unaffected siblings of adults with BD (66). Clinically, a greater severity of WM hyperintensities has been associated with more hospitalizations and poorer response to treatment (67, 68). Furthermore, studies have also found altered WM volume in PFC and limbic structures (29, 69-73). Other WM studies in BD indicate a disruption of anterior limbic circuitry, including prefrontal-striatal and perhaps thalamic pathways, the cerebellum, and medial temporal limbic areas (74, 75). Finally abnormal WM motor pathways such as the corticospinal tract and internal capsule (76, 77) are also reported in BD, and these disruptions may contribute to the symptom of hyperkinesis. Therefore, given the role of prefrontal-striatal circuitry in mood regulation, alterations in the WM linking these areas together could then manifest as mood dysregulation and eventually, fully syndromal BD.

Diffusion tensor imaging (DTI) studies in BD have allowed for a more detailed investigation of how WM tracts are involved in BD. DTI is an MRI based method that measures water diffusion and is most commonly used for the investigation of brain WM structure. Water within a WM tract, is directionally restricted and is often measured as fractional anisotropy (FA). FA is an index of degree of anisotropy of water diffusion in a white matter voxel. Diffusion perpendicular to the axon is restricted by the cell sheath and myelin, and is quantitatively measured as radial diffusivity (RD) (78). Water diffusion is faster along its axis, and is quantitatively measured as axial diffusivity (AD). DTI therefore allows for a 3-dimensional analysis of axonal water diffusion and is a more sensitive measure of WM tract integrity than volumetric measurements.

To date, there are 32 published DTI studies on BD. Of these studies, seven involve children and adolescents. Taken together, DTI studies of both adults (70, 79-100) and youth (76, 101-106) with BD show WM disruptions in the PFC/frontal cortex, the corpus callosum (CC) and association areas (65), including the superior longitudinal fasciculus (SLF) (86, 99, 103), which connects the PFC to the occipital lobe, and in the inferior longitudinal fasciculus (ILF) (99, 106), which connects the temporal to the occipital lobe. Studies in adults with BD have also shown alterations in the uncinate fasciculus, which connects the PFC to subcortical structures, including the amygdala (95, 107).

Despite the importance of the amygdala in emotion regulation and the substantial amygdalar morphometric and functional abnormalities reported in youth with BD, DTI findings have not been as robust for WM tracts

connecting the amygdala to other structures such as the CC and PFC. For example, one study found no DTI differences in WM connecting the subgenual cingulate to the amygdala-hippocampal complex between youth with BD and HC (90). More studies specifically examining white matter tracts connecting amygdala to the PFC need to be conducted in youth, as several studies in adults with BD have reported FA abnormalities in these areas (95, 107, 108).

Other adult BD studies have also found WM differences depending on the subjects' mood state. For example, depressed adult subjects with BD show WM alterations in fronto-limbic connections, CC, cingulum, corona radiata, SLF, and ILF (84, 99). There is also evidence that adults with BD continue to have WM structural differences in these same areas when euthymic (87, 97), suggesting that WM alterations in BD may be state and trait related. In summary, DTI studies in adults and youth with BD have so far shown that microstructural WM abnormalities exist in both cognitive and emotion regulatory pathways.

There are few DTI studies examining youth at high-risk for BD. In a study involving both HR youth (symptomatic with one affected first-degree relative) and those already with BD, both groups showed reduced FA relative to HC in bilateral SLF I, with HR youth having a greater FA value than BD youth (103). In another cross-sectional DTI study of HR youth, Versace et al. (106) found a linear increase with age in FA and a linear decrease with age in RD in HC in the left CC and right ILF. However, in HR offspring a linear decrease in FA and an increase in RD with age were found in the left CC and no relationship was found in the right ILF. These studies suggest that aberrant connections exist in association fibers and the CC in HR youth. These studies also suggest that prefrontal WM changes seen in adults with BD may not develop until later in the course of BD, perhaps after the first manic episode.

Given the findings of widespread WM abnormalities in youth with and at risk for BD, these studies support the concept that abnormal neuronal connectivity is a significant aberrant neurodevelopmental process in BD. However, studies are limited due to varying methodologies and small sample sizes. Combining these studies with other modalities, such as task-activation or resting state fMRI, would demonstrate if indeed functional loss occurs in these altered WM tracts and provide clinical relevance (65, 109). For example, Sui et al. recently examined adults with BD using functional MRI and reported dysfunction in the DLPFC and thalamus with altered WM integrity in the anterior thalamic radiation and uncinate fasciculus, which connects the VPFC to the limbic system (108). As with structural MRI, longitudinal studies are needed to further elucidate how connectivity changes before and after disease onset; as yet there are no published longitudinal DTI studies in youth with or at-risk for BD.

## FUNCTIONAL MRI (FMRI)

FMRI studies examine which areas of the brain respond to particular tasks completed in the MRI scanner, primarily by measuring levels of blood oxygen (BOLD signal) and provide an excellent probe for potential endogenous illness related effects on brain function. Both emotional regulation and cognitive processing have been explored by fMRI studies in PBD. FMRI studies have primarily implicated the PFC, amygdala, and striatum as areas exhibiting abnormal activation patterns in subjects with PBD.

Various types of tasks have elicited abnormal PFC activation in youth with BD. A study using an emotional Stroop paradigm (matching the color of negatively valenced words to the color of either of two adjacent circles) demonstrated *greater* VLPFC activation in *non-euthymic* youth with BD compared with HC (110). In a similar study using the same paradigm, *euthymic* youth with BD showed *reduced* VLPFC and DLPFC activation when matching negatively valenced words (111). These studies suggest that youth with BD experience altered PFC function during cognitive tasks that concomitantly require emotional processing and that mood state may also affect the degree of PFC engagement during these tasks.

The PFC is also abnormally activated in youth with BD during visuospatial working memory tasks that also present emotionally valenced visual stimuli. Youth with BD have been shown to have greater activation than HC in the DLPFC during such a task. In this same study, negatively valenced pictures also invoked greater activation in the DLPFC and other frontal areas over HC (21). Additionally, facial processing tasks have also demonstrated an overactivated PFC. Youth with BD perceived greater hostility and felt more fear to neutral faces than HC and demonstrated greater activation in the VPFC (112). Reduced VLPFC activation when viewing angry and happy relative to neutral faces was also found in youth with BD (113).

Youth with BD also appear to have difficulty engaging the VPFC during tasks that require response inhibition, which is congruent with the difficulties many of these patients have with impulsivity and motor hyperactivity. During an fMRI study where subjects performed a motor inhibition task, youth with BD had decreased VPFC activation compared with HC during failed inhibitory trials (114). In other studies where youth with BD demonstrated successful inhibition, increased DLPFC overactivation compared with HC was shown (115, 116). Youth with BD also activated the DLPFC and primary motor cortex greater than HC in a task requiring response flexibility, suggesting greater activation in DLPFC required to inhibit prepotent responses (117).

Psychotropic medications have also been shown to affect PFC activation. In studies where youth with BD were treated with a second generation atypical antipsychotic, then switched to lamotrigine monotherapy and asked to perform various tasks requiring response inhibition, interference, and working memory, reductions of mania symptoms in BD youth after lamotrigine monotherapy were associated with increased engagement of the ventral medial PFC and the DLPFC (118-120). In the only published study of pre- and post-treatment medication effects on brain activation in HR youth with BD, subjects treated with divalproex showed a correlation between a decrease in depression symptom severity with a decrease in DLPFC activation (121). Medication may therefore help engage the PFC during cognitive tasks in youth with BD, but further studies on the effects of medication on HR youth are needed before clinical conclusions can be drawn.

Collectively, these fMRI studies suggest that children have aberrant PFC engagement prior to and after onset of BD diagnosis. Unlike adult studies which show predominantly DLPFC and VLPFC hypoactivity (122, 123), studies in youth with BD have often shown DLPFC overactivation, indicating that this hyperactivity may be present early in the course of PBD, but then eventually lead to hypoactivity in the setting of subcortical-limbic hyperactivity as an adult, mirroring structural MRI and histopathological findings of decreased DLPFC volume in adults with BD (124).

The PFC, however, is not an isolated structure and has robust connections to other areas relevant to emotional regulation, particularly the amygdala. FMRI studies of the amygdala consistently demonstrate overactivation in youth with BD during face processing and Stroop paradigms. Amygdalar hyperactivity has been shown in youth with BD when viewing neutral faces (125) as well as angry and happy faces (113). Pavuluri et al. used a task in which subjects were asked to judge positive or negative facial expression (directed emotional processing) and determine whether faces showing similar affect were older or younger than 35 years old (incidental emotional processing). Increased amygdalar activation in youth with BD when compared to HC was found during incidental emotional processing relative to directed, suggesting more intense automatic emotional reactivity (126). In addition, amygdalar hyperactivation was also demonstrated in a study using emotionally valenced words in a Stroop paradigm (111). Although not found in all studies, this amygdalar hyperactivity appears to be a fairly consistent finding in youth with BD. Such amygdalar hyperactivity is consistent with the aforementioned findings of decreased amygdalar volume in PBD, as adolescents with BD have demonstrated an inverse correlation between amygdalar hyperactivity and volume (127).

Clinical trials have also found effects of psychotropic medications on amygdalar activation levels. Improvements in depression symptom severity in youth with BD have been correlated with decreased amygdalar activation in response to negatively valenced pictures following an open-label lamotrigine treatment study (118, 128). However, amygdalar overactivation was not reduced in studies of response inhibition, interference, and working memory in youth with BD treated with a second generation atypical antipsychotic and then switched to lamotrigine monotherapy (118-120). Thus it is not yet clear how or in what condition antimanic medications may affect amygdalar function.

The caudate, putamen, and nucleus accumbens comprise the striatum, which is another central part of prefrontal-subcortical circuits involved in mood regulation. The thalamus is also part of this circuit, serving as a relay station between the PFC and subcortical structures. Visuospatial, face processing, and response inhibition tasks have all shown increased activation in these areas in youth with BD. For example, subjects with PBD were found to have greater activation than HC in the left putamen and left thalamus during a visuospatial working memory task. When positively valenced pictures were shown in this same study, greater activation in bilateral caudate and thalamic regions were shown in youth with BD, whereas HC had no activation during the same task (21). In a study where neutral faces were shown, youth with BD perceived greater hostility and felt more fear

when compared to HC and had greater activation in the putamen and nucleus accumbens (125). Similarly, HC showed increased bilateral striatal activation over youth with BD during failed inhibitory trials in a motor inhibition task (114). Youth with BD therefore appear to consistently overactivate striatal structures when presented with emotionally valenced material and during cognitive tasks, suggesting a compensatory mechanism for completing such tasks when compared to HC.

These previous fMRI studies support the idea that neural activation during emotion and cognitive processing is aberrant in PBD. The activation differences observed suggest that youth with BD engage prefrontal, amygdalar, and striatal areas abnormally to accomplish emotional processing and cognitive tasks. Are these independent findings or are they somehow connected? Functional connectivity analyses of fMRI data may help to answer this question. For example, during a task independent resting condition, youth with BD were found to have reduced functional connectivity between DLPFC, superior temporal gyrus, thalamus and striatum compared with HC (129). This abnormal prefrontal-striatal circuitry during rest supports the concept of abnormal *circuits* being central to the neuropathophysiology of BD. These connectivity problems could develop prior to the first manic episode and lead to functional abnormalities before morphometric abnormalities are detected. Future fMRI studies should examine functional connectivity, or blending fMRI with DTI to correlate functional connectivity differences with aberrant white matter connectivity, and focus on asymptomatic and symptomatic youth at high-risk for BD to examine whether there is early functional network impairment that can then be altered by intervention.

## MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Proton magnetic resonance spectroscopy (1H-MRS) is an MRI-based technology that provides quantitative molecular level biochemical information about particular regions of the brain. N-acetyl aspartate (NAA) and creatine (Cr) are healthy nerve cell markers thought to be involved in maintaining fluid balance, energy production, and myelin formation in the brain. PBD studies have shown altered concentrations of these neurometabolites, predominantly in the PFC. Decreased NAA concentrations in the DLPFC and medial PFC were found in three studies of youth with BD (130-132). However, DLPFC NAA levels were found to be normal in youth at high risk for BD, who have not yet had a manic episode (133). This suggests that decreased NAA concentrations in the DLPFC, which is found in adults with BD (134), may develop as the disorder progresses into adulthood. Since NAA is found in healthy neurons, this concept is consistent with the previously mentioned findings of decreased DLPFC activation and volume in adults with BD, a finding that is not consistently found in youth with BD.

Brain myoinositol (mI) is a marker for cellular metabolism and related second messenger signaling pathways and is thought to be involved in myelin sheet and cell membrane synthesis (135); concentrations of mI levels may correlate with myelin turnover. Increased mI concentrations have been reported in the ACC of bipolar manic youth (20, 135, 136) and in the VLPFC of youth with bipolar depression (137). However, studies in adults with BD have found brain mI levels to be decreased (138) or unchanged, compared with HC (20, 139-141). Finally, mI concentrations were reported to be *decreased* in the cerebellar vermis in symptomatic youth at high-risk for BD (142), indicating abnormal cellular metabolism in this area as well, and supporting previous findings of decreased vermal NAA in HR youth (143). The cerebellar vermis is a less studied region that is involved with mood regulation, and has been found to have abnormal volume (23, 144) and activation (21) in adults and youth with BD.

Glutamate is a neurometabolite that may be another useful early indicator for PBD. Studies in children 6-12 years old with BD have found state-dependent increases in glutamate alone or in both glutamate and its precursor storage form, glutamine (together with glutamate referred to as Glx). These findings occurred in the basal ganglia and PFC/frontal lobes (133), in youth with BD with comorbid ADHD (145). This finding was also shown in the ACC in both unmedicated (146) and medicated (147) youth with BD taking risperidone. A recent study of pediatric offspring of parents with BD found decreased absolute glutamate concentrations in the ACC and a trend for decreased glutamate relative to creatinine, but only in youth who had developed fully syndromal mania (148). Therefore, for HR youth, abnormal glutamatergic functioning may again develop only sometime after fully syndromal clinical mania. Some studies have also shown no differences in glutamate concentrations in the DLPFC (130, 149). These discrepant findings could be due to different sampling criteria, varying field strengths, varying protocols for spectral acquisition and analysis, or other confounding variables. Nonetheless, these findings could indicate

abnormal neuronal excitation in the PFC in youth with BD, consistent with the above fMRI findings.

It should be noted that the PBD MRS literature is somewhat difficult to summarize, given discrepant findings and methodologies. For example, some studies report absolute concentrations of metabolites, while others use ratios to creatine. These inconsistencies make it difficult to conclude what the relationship is between PBD and detectable metabolite concentrations. Like fMRI, MRS studies are also limited by state-dependent features of BD (150), and may not represent processes specific to emotion regulation or independent of medication effects. However, while the actual role of these neurochemicals in the development of BD is not yet clear, what is known is that there are aberrations in these neurometabolite levels in key brain regions that as yet provide overall support for the developmental model presented here.

## GENETICS

Family, adoption, and twin studies have clearly indicated that BD is a highly heritable disorder. For example, literature suggests monozygotic concordance rates ranging from 56-80%, while family studies suggest an 80% heritability rate (151).

Moreover, a meta-analysis found that offspring of adults with BD are 4 times more likely to develop a mood disorder compared to children of parents without a psychiatric illness (152). Such "bipolar offspring" have a higher risk than the general population for the development of BD specifically (153, 154), with rates of bipolar spectrum disorders reported in 14-50% in these offspring. Furthermore, family studies suggest that early onset BD is associated with a greater genetic load for BD than for adult onset BD (155, 156).

Because no single gene has been implicated through repeated linkage and genome wide association (GWAS) studies, BD is thought to be a genetically complex disorder caused by a combination of many genes, each conferring a small risk. Through linkage and candidate gene association studies, genes such as those that code for catechol-O-methyltransferase (COMT), GRK 3- BETA, brain-derived neurotrophic growth factor (BDNF), monoamine oxidase (MAOA), the dopamine transporter, the G72/G30 gene (157), and the serotonin transporter (SLC6A4) have all been implicated in adult BD. However, few studies have linked these polymorphisms with pediatric BD. For example, Geller and Cook found no association with COMT (158), the dopamine transporter gene, or the short/long polymorphism of the promoter region of the gene encoding the serotonin transporter (HTT) (159) despite such associations in studies of adults with BD. However, the dopamine D2 receptor (DRD2) gene, a single nucleotide polymorphism (T/T genotype for a T/C) in the glycogen synthase kinase 3-beta (GSK 3-beta) gene, and the polymorphism in the BDNF gene,Val66Met (i.e., where alternative alleles lead to the substitution of valine for methionine in the BDNF molecule) have been significantly associated with early onset BD (160). These findings need replication, as a recent family-based association study found no association of the BDNF met allele, nor the s allele of the 5-HTTLPR or the COMT gene, with a pediatric BD sample (161). Recent GWAS have identified Ankyrin-G (ANK3) and the alpha-1C subunit of the L-type voltage-gated calcium channel (CACNA1C) as susceptibility genes for bipolar disorder in adult samples (162), but as of yet, there have been no studies on these genes in pediatric samples.

Other genetic approaches, such as searching for copy number variants (CNV) specific to early-onset BD, appear to be important for future study of BD now that GWAS have not been conclusive (163). Despite no candidate genes being linked conclusively to early-onset BD, age at onset of BD may be genetically mediated by other methods, Faraone et al. (164) found age of onset of mania to be significantly heritable, and linked to loci on chromosomes 12p (marker D12S1292), 14q (marker GATA31B), and 15q (marker GATA50C). However, a large "mega-analysis" of over 2,000 probands found no association of any single nucleotide polymorphisms with age at onset (165), so genes controlling onset age are still not clear. Phenotypic anticipation, which refers to the increasing disease severity and earlier age of onset of an illness through successive generations, may also have genetic underpinnings. The relationship between anticipation and the existence of expanding trinucleotide-repeat (TNR) sequences have been reported in other disorders such as Huntington's disease and fragile X syndrome. To date, there has been inconclusive evidence regarding TNR expansion associated with anticipation in adults with BD (166).

Thus, although the role of individual genes in the pathophysiology of BD is not entirely clear, BD remains highly heritable, and probably involves many genes that confer risk for the disorder. This risk likely interacts with environmental factors, such as psychosocial

stress, to create pathological responses to stress by way of mood dysregulation and eventually full mood episodes. However, the role of environmental factors on both gene transcription and the onset of pediatric BD remains unclear. Clearly, genes do not confer risk in isolation as most candidate genes implicated in BD code for proteins that regulate neurotransmitters, modulate ion (sodium and calcium) channels, or affect other brain factors. Therefore, they affect brain structure and function/development in specific ways to create risk for BD development. One example of how these susceptibly genes may create risk for BD is the s-allele of the 5-HTTLPR, which is thought to confer small, but clear, increased risk for BD (167). The s-allele has been associated with increased amygdalar activation in healthy adults (168, 169). Thus, overactivation of the amygdala to emotional stimuli in the context of other genetic/neurobiologic risk factors for BD, may eventually lead to full mood episodes and amygdalar/limbic hyperactivity in youth with BD, as described above. Future studies need to investigate how genetic risk factors lead to brain/stress response to create risk for BD. These genes could also moderate other factors involved in stress response, such as inflammation (see below). Such genetic underpinnings are clearly present from birth, but may be regulated differently at various times during development. These genes may interact with environmental factors in epigenetic ways to drive brain development toward or away from the development of mood disorders.

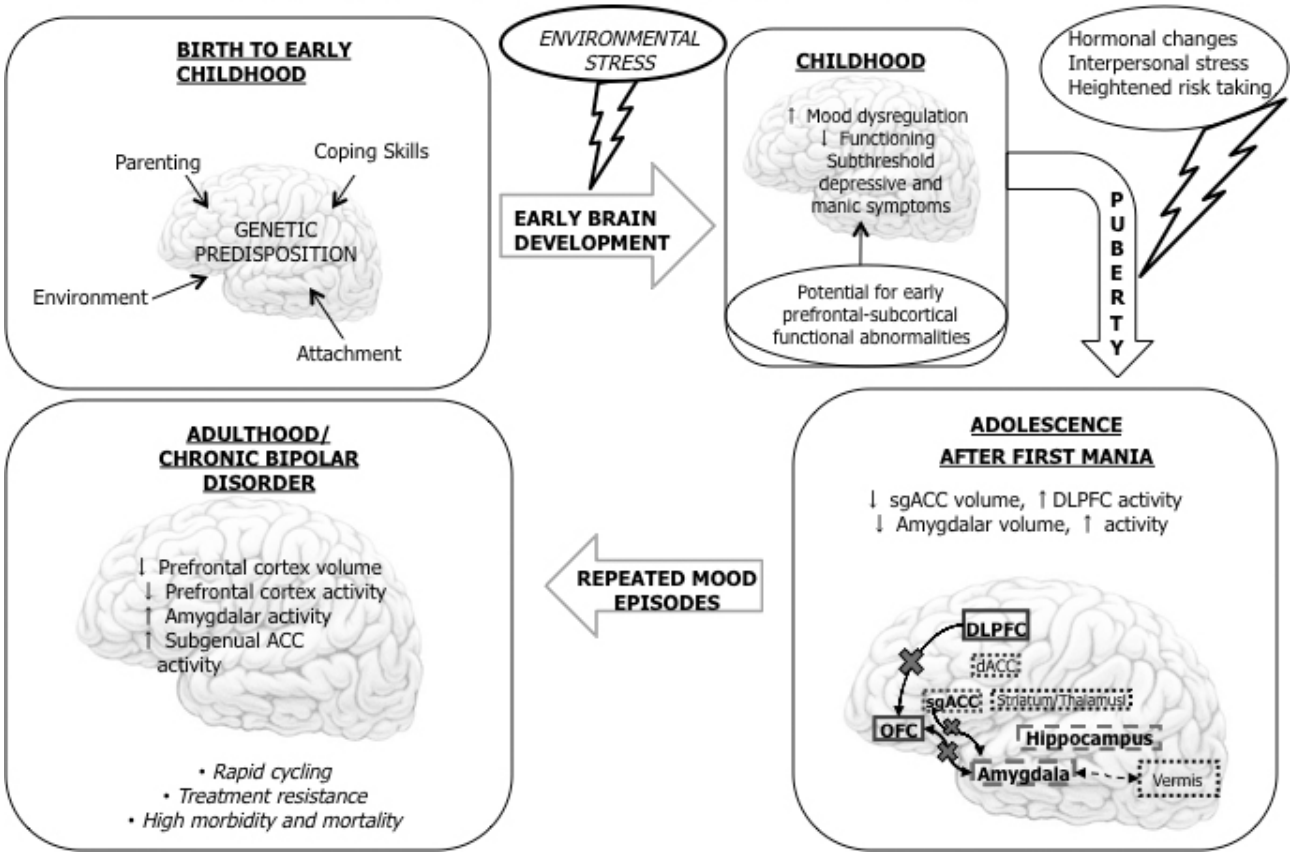
## BIOLOGICAL SERUM INFLAMMATORY MARKERS

The unique sensitivity to psychosocial stressors in individuals with BD may be measured biologically by altered cytokine levels. Cytokines are proteins that promote (pro-inflammatory) or impede (anti-inflammatory) the inflammatory response, and thus indicate internal responses to environmental stressors. Experiencing environmental stressors likely alters the balance of inflammatory response by changing patterns of cytokine secretion (170, 171). Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α are pro-inflammatory cytokines, and IL-10 is anti-inflammatory/immuno-regulatory in nature. During exposure to stress in a laboratory setting, healthy (172-174) and depressed (175) individuals have shown elevated inflammatory cytokines. Furthermore, it is thought that responding to psychosocial life stress alters patterns of cytokine secretion by simultaneously enhancing and suppressing components of the immune system (176). For youth burdened with stressors, secretion of anti-inflammatory/immuno-regulatory cytokines (i.e., IL-10) may be attenuated in favor of pro-inflammatory cytokine (i.e., IL-6, TNF-α) secretion and a high pro-/anti-inflammatory ratio (177).

Studies of adults with BD have so far used cross-sectional, case-control designs and suggest that levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, are elevated while levels of anti-inflammatory cytokines, such as IL-10, are decreased (178). Four studies found increased levels of IL-6 and/or TNF-α during both episodes of mania and depression in individuals with BD compared with controls (33, 179-181). One report found no differences in IL-10 levels between controls and BD patients experiencing mania (182). These findings support that fluctuations in inflammatory cytokine markers are non-specific for the type of mood episode but that symptomatic patients differ significantly from HC. Cytokine levels have not yet been reported in pediatric BD. However, Pandey et al. have preliminary unpublished data finding elevated TNF-α and IF-1beta levels in 22 children and adolescents with BD compared with 21 controls (183). Inflammatory cytokine markers may therefore reflect disease state in those with BD, as stressful life events such as trauma are putative risk factors for BD (184). Further studies showing the relationship between these markers and life stress in youth with and at high-risk for BD are needed to elucidate this relationship.

Because of their effects on neuronal and glial apoptosis, cytokines may be an important mediator in the stress-kindling model of BD development (185). Simeonova et al. previously showed that elevated anxiety, a proxy for stress response, was correlated with decreased hippocampal volume in youth with BD (56). Elevated inflammatory cytokines could be mediating this effect and be detectable at a functional neuronal level. In a recent study, 31 adults showed significant elevations in soluble TNF-alphaRII (receptor) and IL-6 after administration of the Trier Social Stress Test (TSST) (186). The degree of increase of TNF-alphaRii was positively correlated with dorsal ACC and anterior insula activation while performing a social rejection fMRI task. Thus, exaggerated inflammatory response could be linked to both hippocampal atrophy and abnormal activation of limbic areas. Inflammation during brain development has been linked with behavioral abnormalities in animal studies (187, 188). Therefore, it is possible that the abnormal response to stress in at-risk individuals

**Figure 1.** *Putative model for the development and course of early onset bipolar disorder*




leads to inflammatory cytokine states that then adversely affect brain development, resulting in BD symptomatology. Additional studies of inflammatory processes in response to stress in youth with and at risk for BD are needed to test this hypothesis.

## CONCLUSIONS

Our theoretical model for the development of BD in children and adolescents as described in the introduction is based upon several lines of neurobiological evidence drawn from studies employing neuroimaging, genetic, and inflammation-related probes. Children who have genetic loading for BD may express this propensity as a heightened emotional response to stress, seen as amygdalar overactivation and inefficient regulation of subcortical activation by prefrontal structures. Mood dysregulation and psychosocial dysfunction in the context of psychosocial stress then occur. Brain networks responsible for mood regulation may already be developing abnormally, but are further disrupted from normal development and are reinforced into abnormal patterns by repeated pathological emotional responses to stress. Clinically, these disrupted networks, which involve the DLPFC, ACC (dorsal and ventral/subgenual), VLPFC, amygdala/hippocampus, and striatum, may lead to symptoms of depression and mania. Without treatment, children may eventually develop a fulminant manic episode. These children may possess further functional abnormalities such as a lost inverse functional connectivity between the amygdala and the DLPFC. Prolonged and repeated mood episodes may lead to morphometric changes such as deceased amygdalar volume and eventually neurodegeneration of the PFC, which further disrupts crucial prefrontal-subcortical circuits and leads to rapid cycling, treatment resistance, and high morbidity and mortality. Postulated relationships between PFC and subcortical structures as BD advances over the lifetime are illustrated in Figure 1. As seen in this figure, after adolescent first mania, studies have shown increased PFC activation, decreased amygdalar volume with increased amygdalar activation,

and decreased sgACC volume. When adults with BD are imaged, however, both decreased PFC volume and activation is found with increased amygdalar activation and increased sgACC activation. When exactly, however, this transition to adult-type findings in youth with BD occurs is not clear.

Youth at high risk for BD do not show most of the structural and neurochemical changes prior to the onset of a fully syndromal mania. There is a relative lack of structural abnormalities in symptomatic youth at high risk for BD, but as these youth typically have a prolonged prodromal state of subthreshold mood symptoms and functional impairment (189, 190), it is likely that connectivity and functional abnormalities are already present causing current symptomatology and pathological stress response. Thus, it is possible that if underlying functional connectivity and activation abnormalities are addressed early enough, such morphometric changes and neurodegeneration could be prevented. Early interventions may include psychotherapy (191) and medications (60, 192, 193) which have the potential to alter abnormal functional activity and connectivity (121). Further studies examining functional connectivity (combining fMRI with WM correlates via DTI or higher resolution WM mapping methods), resting states, and advanced mapping techniques with genetic and neuroimmune correlates are needed to support, refute, and/or refine the developmental model of BD presented here.

## References


1. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011;68:241-251.
2. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: The Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry 2009;166:795-804.
3. Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006;63:175-183.
4. Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age at onset as a risk factor for poor outcome of bipolar disorder. J Psychiatr Res 2003;37:297-303.
5. Geller B, DelBello MP. Bipolar disorder in childhood and early adolescence. Paperback ed. New York: Guilford, 2003.
6. Geller B, Zimerman B, Williams M, Delbello MP, Bolhofner K, Craney JL, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002;12:11-25.
7. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004;55:875-881.
8. Togen M, Angst, J. Textbook in psychiatric epidemiology. 2nd ed. New York: Wiley-Liss, 2002.
9. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006;63:1139-1148.
10. Berk M, Malhi GS, Hallam K, Gama CS, Dodd S, Andreazza AC, et al. Early intervention in bipolar disorders: Clinical, biochemical and neuroimaging imperatives. J Affect Disord 2009;114:1-13.
11. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994;31:281-294.
12. DelBello MP, Adler CM, Strakowski SM. The neurophysiology of childhood and adolescent bipolar disorder. CNS Spectr 2006;11:298-311.
13. Martinowich K, Schloesser RJ, Manji HK. Bipolar disorder: From genes to behavior pathways. J Clin Invest 2009;119:726-736.
14. Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA, Jr. The neurobiology of the switch process in bipolar disorder: A review. J Clin Psychiatry 2010;71:1488-1501.
15. Pfeifer JC, Welge J, Strakowski SM, Adler CM, DelBello MP. Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2008;47:1289-1298.
16. Adler CM, DelBello MP, Strakowski SM. Brain network dysfunction in bipolar disorder. CNS Spectr 2006;11:312-320; quiz 23-24.
17. Blumberg HP, Martin A, Kaufman J, Leung HC, Skudlarski P, Lacadie C, et al. Frontostriatal abnormalities in adolescents with bipolar disorder: Preliminary observations from functional MRI. Am J Psychiatry 2003;160:1345-1347.
18. Brambilla P, Glahn DC, Balestrieri M, Soares JC. Magnetic resonance findings in bipolar disorder. Psychiatr Clin North Am 2005;28:443-467.
19. Caetano SC, Olvera RL, Glahn D, Fonseca M, Pliszka S, Soares JC. Fronto-limbic brain abnormalities in juvenile onset bipolar disorder. Biol Psychiatry 2005;58:525-531.
20. Cecil KM, DelBello MP, Morey R, Strakowski SM. Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. Bipolar Disord 2002;4:357-365.
21. 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.
22. Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005;162:1256-1265.
23. Monkul ES, Hatch JP, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, et al. MRI study of the cerebellum in young bipolar patients. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:613-619.
24. 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.
25. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. Am J Psychiatry 1999;156:675-682.
26. Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999;56:254-260.
27. Post RM, Weiss SR. A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. Mol Neurobiol 1996;13:33-60.
28. Frazier JA, Breeze JL, Makris N, Giuliano AS, Herbert MR, Seidman L, et al. Cortical gray matter differences identified by structural magnetic

resonance imaging in pediatric bipolar disorder. Bipolar Disord 2005;7:555-569.

29. Chen HH, Nicoletti MA, Hatch JP, Sassi RB, Axelson D, Brambilla P, et al. Abnormal left superior temporal gyrus volumes in children and adolescents with bipolar disorder: A magnetic resonance imaging study. Neurosci Lett 2004;363:65-68.
30. Dickstein DP, Milham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, et al. Frontotemporal alterations in pediatric bipolar disorder: Results of a voxel-based morphometry study. Arch Gen Psychiatry 2005;62:734-741.
31. Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, 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.
32. Chiu S, Widjaja F, Bates ME, Voelbel GT, Pandina G, Marble J, et al. Anterior cingulate volume in pediatric bipolar disorder and autism. J Affect Disord 2008;105:93-99.
33. Kaur S, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Monkul ES, et al. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. Am J Psychiatry 2005;162:1637-1643.
34. 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.
35. Gogtay N, Ordonez A, Herman DH, Hayashi KM, Greenstein D, Vaituzis C, et al. Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. J Child Psychol Psychiatry 2007;48:852-862.
36. Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, et al. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. J Int Neuropsychol Soc 2009;15:476-481.
37. Najt P, Nicoletti M, Chen HH, Hatch JP, Caetano SC, Sassi RB, et al. Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. Neurosci Lett 2007;413:183-186.
38. Moore GJ, Cortese BM, Glitz DA, Zajac-Benitez C, Quiroz JA, Uhde TW, et al. A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. J Clin Psychiatry 2009;70:699-705.
39. Mitsunaga MM, Garrett A, Howe M, Karchemskiy A, Reiss A, Chang K. Increased subgenual cingulate cortex volume in pediatric bipolar disorder associated with mood stabilizer exposure. J Child Adolesc Psychopharmacol 2011;21:149-155.
40. Rajkowska G. Cell pathology in bipolar disorder. Bipolar Disord 2002;4:105-116.
41. 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.
42. Sanches M, Roberts RL, Sassi RB, Axelson D, Nicoletti M, Brambilla P, et al. Developmental abnormalities in striatum in young bipolar patients: A preliminary study. Bipolar Disord 2005;7:153-158.
43. Ahn MS, Breeze JL, Makris N, Kennedy DN, Hodge SM, Herbert MR, et al. Anatomic brain magnetic resonance imaging of the basal ganglia in pediatric bipolar disorder. J Affect Disord 2007;104:147-154.
44. Castellanos FX, Sharp WS, Gottesman RF, Greenstein DK, Giedd JN, Rapoport JL. Anatomic brain abnormalities in monozygotic twins discordant for attention deficit hyperactivity disorder. Am J Psychiatry 2003;160:1693-1696.
45. 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.
46. Liu IY, Howe M, Garrett A, Karchemskiy A, Kelly R, Alegria D, et al. Striatal volumes in pediatric bipolar disorder patients with and without comorbid ADHD. In Review.
47. Garrett A, Chang K. The role of the amygdala in bipolar disorder development. Dev Psychopathol 2008;20:1285-1296.
48. Blumberg HP, Fredericks C, Wang F, Kalmar JH, Spencer L, Papademetris X, et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. Bipolar Disord 2005;7:570-576.
49. Chen BK, Sassi R, Axelson D, Hatch JP, Sanches M, Nicoletti M, et al. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. Biol Psychiatry 2004;56:399-405.
50. 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.
51. Hajek T, Kopecek M, Kozeny J, Gunde E, Alda M, Hoschl C. Amygdala volumes in mood disorders – meta-analysis of magnetic resonance volumetry studies. J Affect Disord 2009;115:395-410.
52. Usher J, Leucht S, Falkai P, Scherk H. Correlation between amygdala volume and age in bipolar disorder – a systematic review and meta-analysis of structural MRI studies. Psychiatry Res 2010;182:1-8.
53. Usher J, Menzel P, Schneider-Axmann T, Kemmer C, Reith W, Falkai P, et al. Increased right amygdala volume in lithium-treated patients with bipolar I disorder. Acta Psychiatr Scand 2010;121:119-124.
54. Geller B, Harms MP, Wang L, Tillman R, DelBello MP, Bolhofner K, et al. Effects of age, sex, and independent life events on amygdala and nucleus accumbens volumes in child bipolar I disorder. Biol Psychiatry 2009;65:432-437.
55. Bearden CE, Soares JC, Klunder AD, Nicoletti M, Dierschke N, Hayashi KM, et al. Three-dimensional mapping of hippocampal anatomy in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2008;47:515-525.
56. Simeonova DI, Jackson V, Attalla A, Karchemskiy A, Howe M, Adleman N, et al. Subcortical volumetric correlates of anxiety in familial pediatric bipolar disorder: A preliminary investigation. Psychiatry Res 2009;173:113-120.
57. Monkul ES, Nicoletti MA, Spence D, Sassi RB, Axelson D, Brambilla P, et al. MRI study of thalamus volumes in juvenile patients with bipolar disorder. Depress Anxiety 2006;23:347-352.
58. Yasar AS, Monkul ES, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, et al. MRI study of corpus callosum in children and adolescents with bipolar disorder. Psychiatry Res 2006;146:83-85.
59. Chen HH, Nicoletti M, Sanches M, Hatch JP, Sassi RB, Axelson D, et al. Normal pituitary volumes in children and adolescents with bipolar disorder: A magnetic resonance imaging study. Depress Anxiety 2004;20:182-186.
60. Chang K, Howe M, Gallelli K, Miklowitz D. Prevention of pediatric bipolar disorder: Integration of neurobiological and psychosocial processes. Ann N Y Acad Sci 2006;1094:235-247.
61. Singh MK, Delbello MP, Adler CM, Stanford KE, Strakowski SM. Neuroanatomical characterization of child offspring of bipolar parents. J Am Acad Child Adolesc Psychiatry 2008;47:526-531.
62. Ladouceur CD, Almeida JR, Birmaher B, Axelson DA, Nau S, Kalas C, et al. Subcortical gray matter volume abnormalities in healthy bipolar offspring: Potential neuroanatomical risk marker for bipolar disorder? J Am Acad Child Adolesc Psychiatry 2008;47:532-539.
63. Karchemskiy A, Garrett A, Howe ME, Adelman N, Simeonova DI, Alegria D, et al. Amygdalar volume in youth at high risk for development of bipolar disorder. Psychiatry Res Neuroimaging 2011, in press.
64. Farrow TF, Whitford TJ, Williams LM, Gomes L, Harris AW. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biol Psychiatry 2005;58:713-723.
65. Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev 2010;34:533-554.
66. Gulseren S, Gurcan M, Gulseren L, Gelal F, Erol A. T2 hyperintensities in

bipolar patients and their healthy siblings. Arch Med Res 2006;37:79-85.

67. Moore PB, Shepherd DJ, Eccleston D, Macmillan IC, Goswami U, McAllister VL, et al. Cerebral white matter lesions in bipolar affective disorder: Relationship to outcome. Br J Psychiatry 2001;178:172-176.
68. Breeze JL, Hesdorffer DC, Hong X, Frazier JA, Renshaw PF. Clinical significance of brain white matter hyperintensities in young adults with psychiatric illness. Harv Rev Psychiatry 2003;11:269-283.
69. Bruno SD, Barker GJ, Cercignani M, Symms M, Ron MA. A study of bipolar disorder using magnetization transfer imaging and voxel-based morphometry. Brain 2004;127:2433-2440.
70. Haznedar MM, Roversi F, Pallanti S, Baldini-Rossi N, Schnur DB, Licalzi EM, et al. Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. Biol Psychiatry 2005;57:733-742.
71. Kieseppa T, van Erp TG, Haukka J, Partonen T, Cannon TD, Poutanen VP, et al. Reduced left hemispheric white matter volume in twins with bipolar I disorder. Biol Psychiatry 2003;54:896-905.
72. McDonald C, Bullmore E, Sham P, Chitnis X, Suckling J, MacCabe J, et al. Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder: Computational morphometry study. Br J Psychiatry 2005;186:369-377.
73. Van der Schot AC, Vonk R, Brans RG, van Haren NE, Koolschijn PC, Nuboer V, et al. Influence of genes and environment on brain volumes in twin pairs concordant and discordant for bipolar disorder. Arch Gen Psychiatry 2009;66:142-151.
74. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry 2005;10:105-116.
75. Green MJ, Cahill CM, Malhi GS. The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. J Affect Disord 2007;103:29-42.
76. Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, et al. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biol Psychiatry 2009;65:586-593.
77. Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, et al. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. Biol Psychiatry 2005;57:448-455.
78. Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 2005;26:132-140.
79. Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, et al. Abnormal frontal white matter tracts in bipolar disorder: A diffusion tensor imaging study. Bipolar Disord 2004;6:197-203.
80. Beyer JL, Taylor WD, MacFall JR, Kuchibhatla M, Payne ME, Provenzale JM, et al. Cortical white matter microstructural abnormalities in bipolar disorder. Neuropsychopharmacology 2005;30:2225-2229.
81. Sussmann JE, Lymer GK, McKirdy J, Moorhead TW, Munoz Maniega S, Job D, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disord 2009;11:11-18.
82. Wang F, Jackowski M, Kalmar JH, Chepenik LG, Tie K, Qiu M, et al. Abnormal anterior cingulum integrity in bipolar disorder determined through diffusion tensor imaging. Br J Psychiatry 2008;193:126-129.
83. Wang F, Kalmar JH, Edmiston E, Chepenik LG, Bhagwagar Z, Spencer L, et al. Abnormal corpus callosum integrity in bipolar disorder: A diffusion tensor imaging study. Biol Psychiatry 2008;64:730-733.
84. Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biol Psychiatry 2011;69:309-317.
85. 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.
86. Chaddock CA, Barker GJ, Marshall N, Schulze K, Hall MH, Fern A, et al. White matter microstructural impairments and genetic liability to familial bipolar I disorder. Br J Psychiatry 2009;194:527-534.
87. Chan WY, Yang GL, Chia MY, Woon PS, Lee J, Keefe R, et al. Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by Tract-Based Spatial Statistics. Bipolar Disord 2010;12:383-389.
88. Delaloye C, Moy G, de Bilbao F, Weber K, Baudois S, Haller S, et al. Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. Int J Geriatr Psychiatry 2011;10: 1309-1318.
89. Haller S, Xekardaki A, Delaloye C, Canuto A, Lovblad KO, Gold G, et al. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. J Psychiatry Neurosci 2011;36:391-401.
90. Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M, 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.
91. Lin F, Weng S, Xie B, Wu G, Lei H. Abnormal frontal cortex white matter connections in bipolar disorder: A DTI tractography study. J Affect Disord 2011;12: 209-306.
92. Mahon K, Wu J, Malhotra AK, Burdick KE, DeRosse P, Ardekani BA, et al. A voxel-based diffusion tensor imaging study of white matter in bipolar disorder. Neuropsychopharmacology 2009;34:1590-1600.
93. McIntosh AM, Munoz Maniega S, Lymer GK, McKirdy J, Hall J, Sussmann JE, et al. White matter tractography in bipolar disorder and schizophrenia. Biol Psychiatry 2008;64:1088-1092.
94. Sprooten E, Sussmann JE, Clugston A, Peel A, McKirdy J, William T, et al. White matter integrity in individuals at high genetic risk of bipolar disorder. Biol Psychiatry 2011; 21: 350-356.
95. Versace A, Almeida JR, Hassel S, Walsh ND, Novelli M, Klein CR, 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.
96. Versace A, Almeida JR, Quevedo K, Thompson WK, Terwilliger RA, Hassel S, et al. Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. Biol Psychiatry 2010;68:560-567.
97. Wessa M, Houenou J, Leboyer M, Chanraud S, Poupon C, Martinot JL, et al. Microstructural white matter changes in euthymic bipolar patients: A whole-brain diffusion tensor imaging study. Bipolar Disord 2009;11:504-514.
98. 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.
99. Zanetti MV, Jackowski MP, Versace A, Almeida JR, Hassel S, Duran FL, et al. State-dependent microstructural white matter changes in bipolar I depression. Eur Arch Psychiatry Clin Neurosci 2009;259:316-328.
100. Zuliani R, Moorhead TW, Bastin ME, Johnstone EC, Lawrie SM, Brambilla P, et al. Genetic variants in the ErbB4 gene are associated with white matter integrity. Psychiatry Res 2011;191:133-137.
101. Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, 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.
102. Barnea-Goraly N, Chang KD, Karchemskiy A, Howe ME, Reiss AL. Limbic and corpus callosum aberrations in adolescents with bipolar disorder: A tract-based spatial statistics analysis. Biol Psychiatry 2009;66:238-244.
103. Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, et al. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disord 2007;9:799-809.
104. James A, Hough M, James S, Burge L, Winmill L, Nijhawan S, et al. Structural brain and neuropsychometric changes associated with

pediatric bipolar disorder with psychosis. Bipolar Disord 2011;13:16-27.

105. Kafantaris V, Kingsley P, Ardekani B, Saito E, Lencz T, Lim K, et al. Lower orbital frontal white matter integrity in adolescents with bipolar I disorder. J Am Acad Child Adolesc Psychiatry 2009;48:79-86.
106. Versace A, Ladouceur CD, Romero S, Birmaher B, Axelson DA, Kupfer DJ, 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, 59 e1.
107. Lin F, Weng S, Xie B, Wu G, Lei H. Abnormal frontal cortex white matter connections in bipolar disorder: A DTI tractography study. J Affect Disord 2011;131:299-306.
108. Sui J, Pearlson G, Caprihan A, Adali T, Kiehl KA, Liu J, et al. Discriminating schizophrenia and bipolar disorder by fusing fMRI and DTI in a multimodal CCA+ joint ICA model. Neuroimage 2011;57:839-855.
109. Wang F, Kalmar JH, He Y, Jackowski M, Chepenik LG, Edmiston EE, et al. Functional and structural connectivity between the perigenual anterior cingulate and amygdala in bipolar disorder. Biol Psychiatry 2009;66:516-521.
110. Passarotti AM, Sweeney JA, Pavuluri MN. Differential engagement of cognitive and affective neural systems in pediatric bipolar disorder and attention deficit hyperactivity disorder. J Int Neuropsychol Soc 2010;16:106-117.
111. Pavuluri MN, O'Connor MM, Harral EM, Sweeney JA. An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. Psychiatry Res 2008;162:244-255.
112. Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, 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.
113. 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.
114. Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 2007;164:52-60.
115. Singh MK, Chang KD, Mazaika P, Garrett A, Adleman N, Kelley R, et al. Neural correlates of response inhibition in pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2010;20:15-24.
116. Strakowski SM, Adler CM, Cerullo MA, Eliassen JC, Lamy M, Fleck DE, et al. Magnetic resonance imaging brain activation in first-episode bipolar mania during a response inhibition task. Early Interv Psychiatry 2008;2:225-233.
117. Nelson EE, Vinton DT, Berghorst L, Towbin KE, Hommer RE, Dickstein DP, et al. Brain systems underlying response flexibility in healthy and bipolar adolescents: An event-related fMRI study. Bipolar Disord 2007;9:810-819.
118. Passarotti AM, Sweeney JA, Pavuluri MN. Fronto-limbic dysfunction in mania pre-treatment and persistent amygdala over-activity post-treatment in pediatric bipolar disorder. Psychopharmacology (Berl) 2011;10: 485-499.
119. Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. Enhanced prefrontal function with pharmacotherapy on a response inhibition task in adolescent bipolar disorder. J Clin Psychiatry 2010;71:1526-1534.
120. Pavuluri MN, Passarotti AM, Parnes SA, Fitzgerald JM, Sweeney JA. A pharmacological functional magnetic resonance imaging study probing the interface of cognitive and emotional brain systems in pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2010;20:395-406.
121. Chang K, Karchemskiy A, Kelley R, Howe M, Garrett A, Adleman N, et al. Effect of divalproex on brain morphometry, chemistry, and function in youth at high-risk for bipolar disorder: A pilot study. J Child Adolesc Psychopharmacol 2009;19:51-59.
122. 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.
123. 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.
124. Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol Psychiatry 2001;49:741-752.
125. Rich BA, Fromm SJ, Berghorst LH, Dickstein DP, Brotman MA, Pine DS, et al. Neural connectivity in children with bipolar disorder: impairment in the face emotion processing circuit. J Child Psychol Psychiatry 2008;49:88-96.
126. 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.
127. Kalmar JH, Wang F, Chepenik LG, Womer FY, Jones MM, Pittman B, et al. Relation between amygdala structure and function in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2009;48:636-642.
128. 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.
129. Dickstein DP, Gorrostieta C, Ombao H, Goldberg LD, Brazel AC, Gable CJ, et al. Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. Biol Psychiatry 2010;68:839-846.
130. Olvera RL, Caetano SC, Fonseca M, Nicoletti M, Stanley JA, Chen HH, et al. Low levels of N-acetyl aspartate in the left dorsolateral prefrontal cortex of pediatric bipolar patients. J Child Adolesc Psychopharmacol 2007;17:461-473.
131. Caetano SC, Olvera RL, Hatch JP, Sanches M, Chen HH, Nicoletti M, et al. Lower N-acetyl-aspartate levels in prefrontal cortices in pediatric bipolar disorder: A (1)H magnetic resonance spectroscopy study. J Am Acad Child Adolesc Psychiatry 2011;50:85-94.
132. Chang K, Adleman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T. Decreased N-acetylaspartate in children with familial bipolar disorder. Biol Psychiatry 2003;53:1059-1065.
133. Castillo M, Kwock L, Courvoisie H, Hooper SR. Proton MR spectroscopy in children with bipolar affective disorder: Preliminary observations. AJNR Am J Neuroradiol 2000;21:832-838.
134. Winsberg ME, Sachs N, Tate DL, Adalsteinsson E, Spielman D, Ketter TA. Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. Biol Psychiatry 2000;47:475-481.
135. Haris M, Cai K, Singh A, Hariharan H, Reddy R. In vivo mapping of brain myo-inositol. Neuroimage 2011;54:2079-2085.
136. Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, et al. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology 2001;24:359-369.
137. Patel NC, Cecil KM, Strakowski SM, Adler CM, DelBello MP. Neurochemical alterations in adolescent bipolar depression: A proton magnetic resonance spectroscopy pilot study of the prefrontal cortex. J Child Adolesc Psychopharmacol 2008;18:623-627.
138. Silverstone PH, McGrath BM, Kim H. Bipolar disorder and myo-inositol: A review of the magnetic resonance spectroscopy findings. Bipolar Disord 2005;7:1-10.
139. Moore CM, Breeze JL, Gruber SA, Babb SM, Frederick BB, Villafuerte RA, et al. Choline, myo-inositol and mood in bipolar disorder: A proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. Bipolar Disord 2000;2:207-216.
140. Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, et al. Brain metabolic alterations in medication-free patients with bipolar

disorder. Arch Gen Psychiatry 2004;61:450-458.

141. Frye MA, Watzl J, Banakar S, O'Neill J, Mintz J, Davanzo P, et al. Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression. Neuropsychopharmacology 2007;32:2490-2499.
142. Singh MK, Spielman D, Libby A, Adams E, Acquaye T, Howe M, et al. Neurochemical deficits in the cerebellar vermis in child offspring of parents with bipolar disorder. Bipolar Disord 2011;13:189-197.
143. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. J Child Adolesc Psychopharmacol 2003;13:545-555.
144. Womer FY, Wang F, Chepenik LG, Kalmar JH, Spencer L, Edmiston E, et al. Sexually dimorphic features of vermis morphology in bipolar disorder. Bipolar Disord 2009;11:753-758.
145. Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, et al. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. Am J Psychiatry 2006;163:316-318.
146. Moore CM, Frazier JA, Glod CA, Breeze JL, Dieterich M, Finn CT, et al. Glutamine and glutamate levels in children and adolescents with bipolar disorder: A 4.0-T proton magnetic resonance spectroscopy study of the anterior cingulate cortex. J Am Acad Child Adolesc Psychiatry 2007;46:524-534.
147. Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, et al. Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: A proton magnetic resonance spectroscopy study of the anterior cingulate cortex. J Affect Disord 2007;99:19-25.
148. Singh M, Spielman D, Adleman N, Alegria D, Howe M, Reiss A, et al. Brain glutamatergic characteristics of pediatric offspring of parents with bipolar disorder. Psychiatry Res 2010;182:165-171.
149. Davanzo P, Yue K, Thomas MA, Belin T, Mintz J, Venkatraman TN, et al. Proton magnetic resonance spectroscopy of bipolar disorder versus intermittent explosive disorder in children and adolescents. Am J Psychiatry 2003;160:1442-1452.
150. Gallelli KA, Wagner CM, Karchemskiy A, Howe M, Spielman D, Reiss A, et al. N-acetylaspartate levels in bipolar offspring with and at high-risk for bipolar disorder. Bipolar Disord 2005;7:589-597.
151. Craddock N, Jones I. Genetics of bipolar disorder. J Med Genet 1999;36:585-594.
152. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: A metaanalysis of risk for mental disorders. Can J Psychiatry 1997;42:623-631.
153. Chang K, Steiner H, Ketter T. Studies of offspring of parents with bipolar disorder. Am J Med Genet C Semin Med Genet 2003;123C:26-35.
154. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. Bipolar Disord 2001;3:325-334.
155. Todd RD. Genetics of early onset bipolar affective disorder: Are we making progress? Curr Psychiatry Rep 2002;4:141-145.
156. Mick E, Faraone SV. Family and genetic association studies of bipolar disorder in children. Child Adolesc Psychiatr Clin N Am 2009;18:441-453, x.
157. Detera-Wadleigh SD, McMahon FJ. G72/G30 in schizophrenia and bipolar disorder: review and meta-analysis. Biol Psychiatry 2006;60:106-114.
158. Geller B, Cook EH, Jr. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. Biol Psychiatry 2000;47:605-609.
159. Geller B, Cook EH, Jr. Serotonin transporter gene (HTTLPR) is not in linkage disequilibrium with prepubertal and early adolescent bipolarity. Biol Psychiatry 1999;45:1230-1233.
160. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH, Jr. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2004;161:1698-1700.
161. Mick E, Wozniak J, Wilens TE, Biederman J, Faraone SV. Family-based association study of the BDNF, COMT and serotonin transporter genes and DSM-IV bipolar-I disorder in children. BMC Psychiatry 2009;9:2.
162. Liu Y, Blackwood DH, Caesar S, de Geus EJ, Farmer A, Ferreira MA, et al. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry 2011;16:2-4.
163. Gershon ES, Alliey-Rodriguez N, Liu C. After GWAS: Searching for genetic risk for schizophrenia and bipolar disorder. Am J Psychiatry 2011;168:253-256.
164. Faraone SV, Su J, Tsuang MT. A genome-wide scan of symptom dimensions in bipolar disorder pedigrees of adult probands. J Affect Disord 2004;82:S71-78.
165. Belmonte Mahon P, Pirooznia M, Goes FS, Seifuddin F, Steele J, Lee PH, et al. Genome-wide association analysis of age at onset and psychotic symptoms in bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2011;156B:370-378.
166. O'Donovan M, Jones I, Craddock N. Anticipation and repeat expansion in bipolar disorder. Am J Med Genet C Semin Med Genet 2003;123C:10-17.
167. Cho HJ, Meira-Lima I, Cordeiro Q, Michelon L, Sham P, Vallada H, et al. Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: A systematic review and meta-analysis. Mol Psychiatry 2005;10:771-781.
168. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science 2002;297:400-403.
169. Von dem Hagen EA, Passamonti L, Nutland S, Sambrook J, Calder AJ. The serotonin transporter gene polymorphism and the effect of baseline on amygdala response to emotional faces. Neuropsychologia 2011;49:674-680.
170. Connor TJ. Don't stress out your immune system - just relax. Brain Behav Immun 2008;22:1128-1129.
171. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: Implications for health. Nat Rev Immunol 2005;5:243-251.
172. Altemus M, Rao B, Dhabhar FS, Ding W, Granstein RD. Stress-induced changes in skin barrier function in healthy women. J Invest Dermatol 2001;117:309-317.
173. Goldman-Mellor S, Brydon L, Steptoe A. Psychological distress and circulating inflammatory markers in healthy young adults. Psychol Med 2010;40:2079-2087.
174. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. Brain Behav Immun 2007;21:901-912.
175. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry 2006;163:1630-1633.
176. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychol Bull 2004;130:601-630.
177. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection and immunopathology. Neuroimmunomodulation 2009;16:300-317.
178. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: A systematic review of the literature. J Clin Psychiatry 2009;70:1078-1090.
179. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 2009;116:214-217.
180. O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in

bipolar affective disorder: Focus on acutely ill patients. J Affect Disord 2006;90:263-267.

181. Ortiz-Dominguez A, Hernandez ME, Berlanga C, Gutierrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: Phasic differences. Bipolar Disord 2007;9:596-602.

182. Liu HC, Yang YY, Chou YM, Chen KP, Shen WW, Leu SJ. Immunologic variables in acute mania of bipolar disorder. J Neuroimmunol 2004;150:116-122.

183. Pandey G, Fareed F, Dwivedi Y, Pavuluri MN. Proinflammatory cytokines in plasma of patients with pediatric bipolar disorder. Presented at 2009 Pediatric Bipolar Disorder Conference, Cambridge, Mass., March 26-27, 2009.

184. Strawn JR, Adler CM, Fleck DE, Hanseman D, Maue DK, Bitter S, et al. Post-traumatic stress symptoms and trauma exposure in youth with first episode bipolar disorder. Early Interv Psychiatry 2010;4:169-173.

185. Bender RE, Alloy LB. Life stress and kindling in bipolar disorder: Review of the evidence and integration with emerging biopsychosocial theories. Clin Psychol Rev 2011;31:383-398.

186. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. Proceedings of the National Academy of Sciences of the United States of America 2010;107:14817-14822.

187. Schafer T, Sperling J, Kollmar O, Richter S, Schilling MK, Menger MD, et al. Early effect of hepatic artery TNF-alpha infusion on systemic hemodynamics and inflammation: A dose-response study in pigs. Int J Colorectal Dis 2010;25:523-532.

188. Stolp HB, Johansson PA, Habgood MD, Dziegielewska KM, Saunders NR, Ek CJ. Effects of neonatal systemic inflammation on blood-brain barrier permeability and behaviour in juvenile and adult rats. Cardiovasc Psychiatry Neurol; Published online 2011. doi:10.1155/2011/469046.

189. Correll CU, Penzner JB, Frederickson AM, Richter JJ, Auther AM, Smith CW, et al. Differentiation in the preonset phases of schizophrenia and mood disorders: Evidence in support of a bipolar mania prodrome. Schizophr Bull 2007;33:703-714.

190. Chang KD. The bipolar spectrum in children and adolescents: Developmental issues. J Clin Psychiatry 2008;69:e9.

191. Miklowitz DJ, Chang KD, Taylor DO, George EL, Singh MK, Schneck CD, et al. Early psychosocial intervention for youth at risk for bipolar I or II disorder: A one-year treatment development trial. Bipolar Disord 2011;13:67-75.

192. DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM. A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. J Clin Psychiatry 2007;68:789-795.

193. Findling RL. Update on the treatment of bipolar disorder in children and adolescents. Eur Psychiatry 2005;20:87-91.