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REVIEW ARTICLE

Using neuroimaging to evaluate and guide pharmacological and psychotherapeutic treatments for mood disorders in children

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Mood disorders are increasing in childhood, and often require multimodal and comprehensive treatment plans to address a complex array of symptoms and associated morbidities. Pharmacotherapy, in combination with psychotherapeutic interventions, is essential for treatment and stabilization. Current evidence supports the use of a number of interventions in children and adolescents diagnosed with DSM-5 mood spectrum disorders, which are associated with impairments in prefrontal–striatal–limbic networks, which are key for emotional functioning and regulation. Yet, little is known about the neurobiological effects of interventions on the developing brain. This chapter provides a synopsis of the literature demonstrating the neural effects of psychotropic medications and psychotherapy in youth with depressive or bipolar spectrum disorders. Additional longitudinal and biological studies are warranted to characterize the effects of these interventions on all phases and stages of mood illness development in children and adolescents.

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Introduction

Children and adolescents are increasingly being diagnosed with mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD). It has been estimated that roughly 1 in 7 youth will experience a mood disorder before age 18.[1] Youth with mood disorders experience the extremes of both negatively and positively valenced emotions, including anhedonia and hopelessness or increased pleasure-seeking and risk-taking.[2] When dysregulated, these emotions may be significant risk factors for the development of a broad range of serious but preventable public health problems among youth, such as substance abuse, pregnancy, accidents, obesity, and suicide.[1,3–8] Importantly, few youth with or at risk for mood disorders receive timely treatment.[9] Indeed, a delay in treatment has been linked to greater symptom severity,[10] functional impairment,[11,12] more frequent emergency room visits,[13] higher healthcare costs,[14] and increased risk for suicide.[15] In spite of vigorous efforts to find effective treatments for mood disorders in youth, treatment challenges are frequent[16] and mood disorders carry high rates of complications, including mortality.[11]

Given the enormous personal and societal costs of pediatric mood disorders, there is a pressing need to develop more targeted interventions and to prevent youth from developing adverse outcomes that can persist over the life course. In general, a multimodal treatment approach that combines pharmacological agents and psychosocial interventions is suggested, with the goals being to improve symptoms, to provide psychoeducation, to promote treatment adherence, to prevent relapse, and to attenuate long-term complications.[16,17] Clinicians are encouraged to advocate for prevention, early intervention, and biopsychosocial treatments that promote healthy growth and development in any cultural context.[17–19] At this point, however, we know relatively little about the mechanisms that underlie treatment in youth and presume that the effects of pharmacological and nonpharmacological interventions are multifactorial.

Researchers have consistently documented impairments in emotional functioning and emotion regulation (ie, how people respond to their own emotions[20]) in youth with mood disorders.[2,21] Moreover, these difficulties have been

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found to predict the early onset[22] and the recurrence[23,24] of mood episodes, which suggests that impairments in specific domains of emotional functioning reflect stable vulnerabilities that place individuals at increased risk for experiencing recurrent mood episodes. Neuroimaging and other studies in pursuit of biomarkers of mood disorders have complemented these clinical findings,[25] and have documented aberrant structure, function, and connectivity in brain regions that subserve these aspects of emotion and emotional regulation,[26] along with key molecular (eg, mitochondrial dysfunction) and genetic vulnerabilities for mood symptoms in youth.[27] Specifically, investigators have reported structural anomalies in pediatric mood disorders in the amygdala and hippocampus, and functional abnormalities in the ventrolateral (VLPFC) and dorsolateral prefrontal cortex (DLPFC), amygdala, and ventral striatum.[28] There is also growing recognition that youth with mood disorders are characterized by abnormalities in the anatomical and functional connections among these prefrontal and limbic brain regions.[29,30] Importantly, dysregulated activity in these emotion-based neural circuits has been shown to be modulated by pharmacological agents that may enhance neuronal resilience and plasticity to prevent the progression of mood disorders.[31] However, the underlying neural mechanisms of intervention in pediatric mood disorders remain elusive. Investigating such mechanisms could provide promising targets for novel experimental therapeutics in the treatment of mood disorders and provide greater insight into the neurobiological basis of mood disorders during childhood.[31]

One way to elucidate neural mechanisms that underlie the effects of treatment in mood disorders is to use magnetic resonance imaging (MRI) to assess in vivo brain differences in youth before and after an intervention has occurred. For example, specific differences in brains exposed versus unexposed to medications may suggest biological pathways through which treatments are functioning to reduce symptom burden. In a review of neuroimaging studies of both youth and adults with BD, for example, medications were found to have either no effect or a normalizing effect on brain MRI findings in clinical samples compared to healthy subjects.[32,33] Some neuroimaging studies have attempted to examine the effects of medications on brain structural and functional outcomes in post-hoc analyses, and have not consistently found medication exposure to confound structural,[34] functional,[35,36] or neurometabolite[37] findings. In other studies, researchers have tried to avoid the potential confounding effects of medications on brain MRI results altogether by studying only unmedicated or medication naive youth.[38–41] While there are some clear advantages to examining unmedicated youth, youth with a mood disorder who are medication naive are difficult to find and may represent a subset of the population with relatively low symptom severity, thereby limiting generalizability of the results to the overall population.

We will review structural, functional, neurochemical, and other neuroimaging modalities employed to study the neurophysiological alterations associated with psychotropic medication exposure in youth with depressive and bipolar disorders. In addition, we will review neuroimaging studies that have examined the effects of psychotherapeutic interventions for pediatric mood disorders to explore effects of nonpharmacological interventions on the brain. We will illustrate that interventions during childhood do indeed affect brain structure and function, and we will propose areas of future study that will further explain the biological correlates of treating mood disorders in childhood.

Disorders Studied

Depressive disorders

Youth with depressive disorders demonstrate abnormalities in brain structure, function, and connectivity in key prefrontal and subcortical striatal and limbic brain regions.[29] For example, studies of youth with MDD have consistently found reductions in hippocampal volume detected as early as the preschool years,[42] and in young offspring of mothers with depression even before the onset of symptoms.[43] Across tasks assessing emotion processing, cognitive control, affective cognition, reward processing, and resting state, researchers have found elevated neural activity in the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex (OFC), and amygdala in children and adolescents with MDD.[44] These disruptions in the prefrontal–striato–limbic neural circuit are consistent with current developmental conceptualizations of MDD as a disorder of disrupted emotional functioning and emotion regulation.[45]

While effective treatments are available, the impact of treating depression on the brain in youth is understudied. In the only longitudinal functional MRI (fMRI) study that has examined changes in prefrontal and limbic brain activity with treatment in pediatric depression, Tao *et al* showed that after 8 weeks of open-label fluoxetine treatment, 19 depressed youth with baseline overactivation in prefrontal and limbic regions showed normalization of brain activation in these areas.[46] Further region-of-interest analyses of the areas involved in emotion processing indicated that before treatment, depressed youths had significantly greater activations to fearful relative to neutral facial expressions than did healthy comparison subjects in the amygdala, orbitofrontal cortex, and subgenual anterior cingulate cortex bilaterally. Fluoxetine treatment appeared to decrease activations in all 3 regions. This study is limited by the lack of a placebo arm to substantiate that fluoxetine was responsible for normalizing activations in these regions, as opposed to nonspecific factors such as time.

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A smaller open-label study evaluated the potential neurochemical benefit of supplementing fluoxetine with creatine for 8 weeks in 5 adolescent females who had been stabilized on fluoxetine but continued to have persistent depressive symptoms.[47] This study used phosphorus magnetic resonance spectroscopy (MRS) in 9 voxels from a 25-mm slice located at the corpus callosum, anterior commissure, and posterior commissure, and found that compared to healthy controls, creatine-supplemented adolescents demonstrated a significant increase in brain energy metabolism, as measured by phosphocreatine (PCr) concentration, on follow-up MRS brain scans. This study supports multiple lines of evidence that implicate mitochondrial dysfunction in the pathophysiology of mood disorders, but the study warrants replication due to its small sample size and lack of a placebo control group.

Forbes *et al* collected fMRI scans during a monetary reward task in adolescents with MDD at baseline to predict clinical response to an 8-week open trial using either cognitive behavioral therapy (CBT) or CBT plus selective serotonin reuptake inhibitor (SSRI).[48] Using growth modeling to examine change in clinical characteristics and its association with brain function, they found that severity, anxiety symptoms, and depressive symptoms decreased over treatment. However, final levels of severity and anxiety symptoms, but not depressive symptoms, were associated with pretreatment striatal reactivity, and rate of anxiety symptom reduction was associated with greater striatal reactivity and lower medial prefrontal cortex reactivity. These results emphasize the importance of comorbid symptom severity in brain functional responses, and the need to address clinical heterogeneity in depression when developing interventions. This study seeks to provide a translational use of neuroimaging as a way to choose the most effective individualized treatments for patients.

Transcranial magnetic simulation (TMS) paradigms may also be useful to identify which youth with depression are more likely to respond to intervention based on neurophysiological mechanisms. A recent study reported on the use of the paired-pulse TMS to noninvasively measure baseline levels of cortical inhibition in 16 children and adolescents with depression preceding a 6-week course of fluoxetine treatment.[49] Eight youth in this study were treatment-responsive to fluoxetine, whereas 8 youth were nonresponsive. Youth in this study who were nonresponsive to fluoxetine had evidence of poor cortical inhibition and impaired $GABA_B$ functioning, which is consistent with prior studies that have demonstrated the modulatory effects of antidepressants on $GABA_B$ receptors. This study provides further specificity of current models of prefrontal inhibitory dysfunction in pediatric depression[50] implicating $GABA_B$ in the pathophysiology of MDD in youth and in mechanisms of SSRI response. Additional neuroimaging studies are needed to investigate both the baseline predictors of response to these treatments and the neural effects of widely accepted pharmacological and psychotherapeutic treatments for pediatric depression.

Bipolar disorders

The neural effects of pharmacological intervention in youth with BD have been more extensively studied. Bipolar symptoms are often severe in youth and create a significant level of impairment such that it is challenging to find youth who are unmedicated for this disorder when they are enrolled in a neuroimaging study. Like youth with MDD, youth with BD commonly demonstrate abnormalities in brain structure, function, and connectivity in key prefrontal and subcortical striatal and limbic brain regions that are involved in emotional functioning and regulation.[51] Some treated youth with BD do not show significant departures from healthy development in brain structure and function, possibly due to the normalizing effects of medication. Researchers have used 4 main methods, either post-hoc or a priori, to evaluate the neural effects of medication in pediatric BD. First, researchers have examined youth with BD who received neuroimaging regardless of treatment exposure and have compared subsamples of youth post-hoc with and without medication exposure. Second, researchers have compared neuroimaging outcomes among youth with a variety of different medication exposures. Third, studies have added neuroimaging to open label and randomized controlled clinical trials to directly measure neural effects of medication during a clinical trial. Finally, researchers have compared neural function in treatment responders versus nonresponders and across multiple MRI modalities. Each of these approaches to understanding the neural effects of psychotropic medications has limitations and strengths. We will provide examples of each of these approaches in turn, with the goal of summarizing the current state of the field.

Structural and functional MRI studies in pediatric BD have shown mixed results in terms of differences in volumes and activations in key prefrontal and limbic regions in youth exposed and unexposed to medication. Adolescents with BD who were exposed to lithium have larger right hippocampal volumes than those who were unexposed to lithium.[52] Youth with BD who had past mood stabilizer exposure (either lithium or divalproex) have shown significantly greater posterior subgenual anterior cingulate cortex[53] and amygdala[54] volumes compared to BD youth without mood stabilizer exposure and healthy subjects. The effects on white matter microstructure have been less studied, with one post-hoc analysis finding no effects of medication exposure on diffusion tensor imaging (DTI) findings in pediatric BD.[55] Finally, unmedicated and

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medicated youth with BD showed similar reductions in ventrolateral prefrontal cortex and striatal activations relative to controls during unsuccessful motor inhibition.[56] Replication studies with larger subsamples of youth exposed and unexposed to medications evaluated over longer periods of time would clarify these mixed results.

Differential neural effects between 2 medications have also been demonstrated. Pavuluri *et al* investigated the relative effects of risperidone and divalproex on prefrontal–striatal–limbic neural circuits during 3 different cognitive tasks in unmedicated manic patients randomized to either treatment and healthy subjects.[57–59] In the first color-matching task, participants matched the color of a positive, negative, or neutral word with 1 of 2 colored circles. They found that after treatment and relative to healthy subjects, the risperidone-treated group showed increased activation in the right pregenual and subgenual ACC, and decreased activation in the bilateral middle frontal gyrus; left inferior, medial, and right middle frontal gyri; left inferior parietal lobe; and right striatum. In the divalproex-treated group, relative to healthy subjects, increased activations were found in the right superior temporal gyrus, left medial frontal gyrus, and right precuneus. In the second response inhibition task, a motor response already "on the way" to execution had to be voluntarily inhibited on trials where a stop signal was presented.[58] Youth taking risperidone and divalproex differentially engaged an evaluative affective circuit (EAC; bilateral inferior frontal gyrus, middle frontal gyrus, ACC, middle temporal gyrus, insulae, caudate, and putamen) during this task. Within the EAC, post-treatment and relative to healthy subjects, greater engagement was seen in left insula in the risperidone group and left subgenual ACC in the divalproex group. Finally, during a working memory task under emotional duress, divalproex enhanced activation in a fronto-temporal circuit, whereas risperidone increased activation in the dopamine (D_2) receptor-rich ventral striatum.[59] These studies illustrate that the differential effects of psychotropic medications on the brain may be task-dependent and regionally specific. Future comparative pharmacological MRI studies must strive to examine the mechanisms that underlie differential neural targets by various psychotropic medications.

Researchers have examined the effects of pharmacological intervention on prefrontal–striatal–limbic fMRI activation in youth with BD using prospective studies. The first study was an open-label study by Chang *et al*[60] that examined the neural effects of lamotrigine in adolescents with bipolar depression. It found that BD youth treated with lamotrigine for 8 weeks had less amygdala activation when viewing negative stimuli as depressive symptoms improved; whether the changes in fMRI activation were due to lamotrigine exposure or to improvements in depressive symptoms (as a consequence of lamotrigine treatment) could not be determined. Pavuluri *et al* examined unmedicated youth with BD after open label treatment with a second-generation antipsychotic (SGA) followed by adjunctive lamotrigine monotherapy, and compared fMRI activation to that of healthy subjects while performing an affective color matching task.[61] Pavuluri *et al* also observed treatment-related decreases in the VMPFC and the dorsolateral prefrontal cortex (DLPFC) in BD youth. In addition to normalizing symptoms, treatment with an SGA followed by lamotrigine monotherapy also enhanced ventrolateral prefrontal cortical (VLPFC) and temporal lobe activity during response inhibition,[62] and increased prefrontal cortical and cognitive regional activation but did not normalize amygdala overactivation relative to healthy subjects during affective working memory.[63] Improvement on the Young Mania Rating Scale (YMRS) score significantly correlated with decreased activity in the VMPFC within the patient group, suggesting a normalizing effect of treatment on fMRI activation, which may either be due to direct medication effects on the brain or due to symptomatic improvement. The neuroimaging study with the longest follow-up period collected fMRI scans of patients with pediatric BD at baseline, at 16 weeks, and after 3 years of pharmacotherapy.[64] This study found that BD youth had baseline hyperactivation in the DLPFC, VLPFC, and amygdala during an affective color-matching task. DLPFC activation normalized by 16 weeks, but the VLPFC, ACC, amygdala, and striatum normalized by the 3-year follow-up. This study suggests that the DLPFC may respond more quickly to medication than do the other regions tested. A randomized, controlled design may be better suited to determine whether neural change that is observed from pre- to post-medication exposure is related to symptomatic improvement or to the direct effects of the psychotropic agent.

One randomized controlled trial compared neural activation in a priori regions of interest defined by Brodmann areas (BA) during a sustained attention task in 23 youth with BD randomized to ziprasidone versus placebo and 10 healthy comparison youth at baseline, at day 7, and at day 28 post-treatment.[65] Compared with placebo, treatment with ziprasidone was associated with greater increases over time in right ventral prefrontal (BA 11 and 47) activation. Interestingly, these effects were not associated with differences in symptom improvement between the treatment groups, suggesting that the observed neural effect of ziprasidone is independent of indices of symptom improvement. However, patients who subsequently responded to ziprasidone showed significantly greater deactivation in the right BA 47 at baseline than those who did not respond to ziprasidone. Increases in right BA 11 and 47 activation observed during tasks of sustained attention following ziprasidone suggest that ziprasidone may at least partially correct prefrontal

dysfunction in currently manic youth. These findings represent the first placebo-controlled evidence for neurofunctional effects of pharmacological treatment in youth with mania.

Other studies have looked at the effects of pharmacotherapy on broad neurocognitive prefrontal–striatal–limbic networks in pediatric BD. Wegbreit *et al* aimed to determine functional connectivity differences in youth with BD who were responders ($n = 22$) versus nonresponders ($n = 12$) to 1 of 3 mood stabilizing medications (divalproex, risperidone, or lamotrigine) and as compared to healthy controls ($n = 14$).[66] During a color-matching task, a frontolimbic network was identified that showed impaired functional integration in youth with BD relative to healthy subjects when participants viewed negatively valenced words. Medication responders in the group with BD showed greater connectivity of the amygdala into the network before and after treatment compared with nonresponders, with responders showing a pattern more similar to healthy subjects than to nonresponders. The degree of amygdala functional connectivity predicted medication response as well as the improvement in YMRS scores across responders and nonresponders regardless of medication type. Authors inferred from these results that increased functional integration of the amygdala within the frontolimbic network might be a predictor of broad responsivity to mood stabilizers in BD. However, the specific effects of mood stabilizers on task-based or intrinsic functional connectivity patterns associated with pediatric BD have yet to be investigated.

In a multimodal neuroimaging study, Chang *et al*[67] examined the effects of divalproex on prefrontal and limbic structure, chemistry, and function in 11 symptomatic youth with mood dysregulation at high risk for BD, who were scanned at baseline and after 12 weeks of divalproex treatment. There were no detectable effects on brain structure or neurochemistry after 12 weeks of open label treatment with divalproex or relative to 6 typically developing healthy controls. However, decreases in DLPFC activation while processing negatively versus neutrally valenced International Affective Picture System (IAPS) pictures correlated with decreases in depressive symptom severity.[67] Thus, consistent with prior studies suggesting DLPFC dysregulation during emotion processing in pediatric BD,[68,69] prefrontal activation during negative emotional processing was found to be associated with depression symptom severity in high-risk youth with mood dysregulation. However, it is unclear from this study whether decreased DLPFC activation from baseline to 12 weeks post-treatment during emotion processing is due to the intermediate effects of symptom improvement or due to the direct effects of divalproex. To disentangle these etiologies for the change in brain function, future studies need to consider alternative research designs that temporally distinguish a neural response to intervention from symptom improvement (eg, by including intermediate scans between baseline and follow-up to determine whether neural changes precede and mediate treatment response).

Other studies have used MRS to investigate medication effects on neurometabolite concentrations in key prefrontal cortical regions that are important for emotion regulation. Neurometabolites studied in pediatric BD include N-acetyl aspartate (NAA) and phosphocreatine/creatine (PCr/Cr), healthy nerve cell markers that are putatively involved in maintaining energy production and myelin formation in the brain,[70] and myo-inositol (mI) levels, a marker for cellular metabolism and second messenger signaling pathways. Both NAA and mI concentrations have been shown to be responsive to lithium treatment in some[71,72] but not all[73] pediatric BD studies. Specifically, Davanzo *et al*[71] found that after 1 week of acute lithium treatment, levels of mI/creatine ratios (mI/Cr) in the ACC decreased; this response was stronger for lithium responders than for lithium nonresponders. However, Patel *et al*[73] did not find any acute (1 week) or chronic (42 days) lithium effects on mI levels in the medial and lateral prefrontal cortices. In a different study, Patel *et al* found that after 42 days of lithium administration, adolescents with BD showed reductions in NAA concentration in the VMPFC.[72] There was a time-by-remission-status interaction of NAA concentrations in the VMPFC, such that youth who remitted developed decreased mean NAA concentration from day 7 to day 42, whereas nonremitters showed an increase in mean NAA concentration during that same time period. The authors speculated that higher lithium levels earlier in the treatment course might have resulted in lithium-induced increases in prefrontal metabolism.[72] These findings suggest that lithium exerts its therapeutic effect,[74] either by increasing cellular fluid shifts or by modulating intracellular calcium signaling pathways to deplete membrane inositol lipids.[75,76] Thus, some but not all prior studies have demonstrated that alterations in neurometabolite concentrations may explain the pathophysiology of BD[77] and may be sensitive to the effects of psychotropic medications in this population.

Prefrontal neurometabolite levels in youth have also been examined after treatment with divalproex[67] and the atypical antipsychotic olanzapine.[78] In a cohort of youth at high-risk for developing BD, there were no statistically significant changes in pre- to post-divalproex NAA to Cr (NAA/Cr) ratios, but there was a large effect size ($d = 0.94$) for a decrease in right dorsolateral prefrontal NAA/Cr after treatment with divalproex.[67] This post-treatment *decrease* rather than an expected increase in the NAA/Cr ratio was surprising, given the previously proposed neurogenic effects of divalproex leading to

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increases in NAA.[79] This study may have also been limited by a small sample size, inadequate dose range,[80] short exposure to divalproex, or lack of significant neurobiological impact of divalproex on the neurochemistry of BD youth. Hospitalized adolescents with bipolar I disorder who were experiencing a manic or mixed episode achieved remission with olanzapine and demonstrated increases in ventral prefrontal NAA as compared to nonremitting patients, who showed decreases in prefrontal NAA concentrations.[78] Neurogenic effects of these mood stabilizing agents have been proposed in rat brains[81] and neural stem cells,[82] providing a cellular-level explanation for treatment-related neurometabolite changes.

Prefrontal glutamate, its precursor and storage form glutamine, and the combination of glutamate and glutamine (Glx), have also shown treatment-related changes in pediatric BD. Moore *et al* used ^{1}H-MRS to show decreased levels of glutamine in the ACC in unmedicated youth with BD as compared to healthy subjects and medicated youth taking various psychotropics.[83] They also found that unmedicated children with BD and significant manic symptoms had lower Glx to creatine (Glx/Cr) ratios in the ACC compared to children with BD who were stably treated with risperidone.[84] Mania severity correlated negatively with ACC Glx/Cr levels.

Taken together, these studies suggest that medications appear to have an overall normalizing effect on prefrontal, striatal, and limbic structure, function, and neurometabolites in youth with or at risk for BD. Findings from these studies support that medications used to treat BD symptoms may restore volumetric deficits and improve functional activity in ventrolateral and medial prefrontal regions critical for emotional functioning and regulation. In general, youth with BD show decreased activity in amygdala after treatment for mania or depression. In the few instances when increases in amygdala activation relative to healthy subjects were observed regardless of treatment response, authors suggested that residual amygdala hyperactivity may be a trait-like abnormality that may be less responsive to pharmacological intervention.[85] Medications also affect neurometabolite levels in emotion-relevant regions, which may represent either an intermediate or independent mechanism through which brain function is modulated.

Three neuroimaging studies have examined the effects of nonphamacological treatments on brain function in regions and networks that are critical for emotional function and regulation. One study looked at the effects of psychotherapy on brain activation during response inhibition in youth with BD in a depressed mood state.[86] Ten adolescents performed a response inhibition task during fMRI scanning before and after 6 weeks of psychotherapy combined with medication, and were compared to 10 healthy controls. At baseline, BD adolescents, compared to healthy controls, had higher VLPFC and superior temporal activation during response inhibition. After treatment, depression symptoms decreased, and activation increased in the hippocampus and thalamus, but changes in activation were not correlated with changes in symptoms. In another fMRI study of the same sample, this time scanned while viewing facial expressions, psychotherapy resulted in increased activation to happy faces in the insula, cerebellum, and VLPFC, although these changes were not associated with changes in depressive symptoms.[87] Finally, a recent study showed that following psychotherapy, youth at risk for BD had decreased activation in the amygdala and increased activation in the DLPFC.[88] Importantly, increased DLPFC activation correlated with decreases in symptoms of mania, and changes in DLPFC activation following therapy served to normalize activation in this area compared to matched healthy controls. These studies provide exciting initial evidence that psychotherapeutic interventions can have normalizing effects on the neural circuit abnormalities implicated in pediatric BD.

Overall, these findings are consistent with those reported in adults with BD,[33] which have suggested neurogenic effects of lithium in brain structures important for emotion regulation. Few cross-sectional studies have shown significant post-hoc effects of medication on brain structure compared to brain function,[33] although rigorous analyses have not been possible when the majority of subjects were medicated. Medication effects have also been more frequently observed in longitudinal studies designed to assess the impact of particular medications on brain function. With a few exceptions, the observed effects were normalizing, meaning that treated individuals with BD were more similar than their untreated counterparts to healthy subjects. Larger controlled studies that examine youth starting prior to intervention would aid in understanding the specific long-term effects of intervention on neural structure and function in BD.

Discussion

Neuroimaging studies have shown great promise to advance our understanding of potential mechanisms of action of effective treatments for childhood onset mood disorders. Reassuringly, in these initial studies, intervention appears to have a normalizing effect on brain structure and function, particularly in the regions and networks that are critical for emotional functioning and regulation. For example, the neurotrophic effects of lithium on amygdala and hippocampal volumes are also correlated with symptom improvement. In addition, there appears to be normalization of structure and functional activations while performing a wide array of

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neurocognitive tasks after treatments with antidepressants, atypical antipsychotics, and mood stabilizers. Additional information is needed to better understand the critical periods of benefit from these interventions, and how they compare relative to one another. Longitudinal studies that track youth well into adulthood will also provide important supporting evidence for the long-term beneficial effects or deleterious consequences of treatment.

It is also clear from this review that using neuroimaging tools to probe intervention effects in pediatric mood disorders may be associated with unique methodological challenges. These include the unknown test–retest reliability of neuroimaging data, determining whether we can associate brain changes with etiological disease factors, and how to attribute a causal link between intervention effects and changes in brain measures.[89] Future studies should be designed with placebo arms to distinguish these related but separate effects on brain structure and function. Demonstrating significant correlations between changes in symptoms and changes in activation also can help to clarify the meaning of the results. In addition, the study of treatment effects in pediatric mood disorders presents additional unique challenges due to variance in brain maturation, analysis methods, and the potential for motion artifacts. Methodological advancements are needed to minimize confounds associated with artifact and to optimize analytical techniques to enable predictive inferences. Finally, interventions reviewed here were for youth in need of them rather than for typically developing healthy youth who were experimentally exposed to these interventions, which would be ethically challenging.

There are many justifiable concerns about the adverse effects of interventions such as psychotropic medications on the developing body and brain of youth. These medications may clearly have adverse peripheral effects on the body, of which the long-term effects are not clear, and may also have central adverse effects, such as extrapyramidal symptoms and sedation. However, we know from prospective observations that the levels of morbidity and mortality from mood disorders are very high if left untreated. Thus, while adverse effects could arise, these need to be balanced by the potential *beneficial* effects, both behavioral and neurochemical. A comprehensive investigation that evaluates both risks and benefits of intervention is certain to substantiate why behavioral and functional improvements are observed at the clinical level. Moreover, it would be important to determine both predictors of response as well as predictors of adverse effects. For example, neuroimaging may help determine which youth offspring of parents with BD who are being treated for anxiety or depression will respond well to SSRIs and which would have a high likelihood of developing antidepressant-induced mania.[90]

When we learn more about the effects of treatment on brain structure and function, and if there is a particular window during development in which they are optimally used (or most problematic), we can develop more targeted approaches to treatment. This knowledge can serve as a guidepost for the next generation of studies and build on emerging treatment biosignatures to personalize interventions for youth with or at risk for mood disorders.[85] The possibility remains that acute intervention with proper medications at a critical point in time will allow for shorter duration of treatment needed, and potential neuroprotection or neuroplastic changes that will then eliminate the need for a lifetime of medications. All practitioners caring for youth with or at risk for mood disorders should be concerned that these youth achieve full and permanent remission of all symptoms and are able to eventually be taking as few medications as possible, if any, prior to reaching adulthood.

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