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Toward Dysfunctional Connectivity: A Review of Neuroimaging Findings in Pediatric Major Depressive Disorder

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Abstract

Child and adolescent psychiatric neuroimaging research typically lags behind similar advances in adult disorders. While the pediatric depression imaging literature is less developed, a recent surge in interest has created the need for a synthetic review of this work. Major findings from pediatric volumetric and functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI) and resting state functional connectivity studies converge to implicate a corticolimbic network of key areas that work together to mediate the task of emotion regulation. Imaging the brain of children and adolescents with unipolar depression began with volumetric studies of isolated brain regions that served to identify key prefrontal, cingulate and limbic nodes of depression-related circuitry elucidated from more recent advances in DTI and functional connectivity imaging. Systematic review of these studies preliminarily suggests developmental differences between findings in youth and adults, including prodromal neurobiological features, along with some continuity across development.

Keywords

pediatric depression; major depressive disorder; adolescents; neuroimaging; MRI brain imaging; fMRI

Introduction

Pediatric major depressive disorder (MDD) is associated with a four-fold risk of recurrence in adulthood and predicts long-term depression and adult functional impairment (Pine, Cohen goo 1998). Suicide, which occurs at a higher rate among depressed youth compared to adults, is the fourth leading cause of death for youth aged 10–14, and the third leading cause of death for youth aged 15–24 (CDC 2007), underscoring the need for an appropriate neurobiological understanding of depression in youth. In addition, the study of neurobiology of depression during childhood and adolescence is necessary for understanding of the adult form, because at this early stage, confounds from the natural course of illness and treatment interventions are minimized. Further, given ongoing development of the neural substrates relevant to emotion (Benes, Turtle et al. 1994; Giedd, Snell et al. 1996; Giedd, Vaituzis et al. 1996; Giedd, Blumenthal et al. 1999; Cunningham, Bhattacharyya et al. 2002), examination of the pathophysiology of unipolar depression in youth may reveal a role for aberrant developmental processes that lead to depressive pathology, with mechanisms that differ developmentally from those found in adult-onset depression. Increased neuronal plasticity prior to adulthood may hold promise for appropriate interventions to alter negative trajectories. Therefore, a clear understanding of the neural basis for abnormal emotional processing early in the development of major depression will be essential for shaping effective early interventions.

Brain imaging has revolutionized psychiatric research with its capacity to examine *in vivo* brain structure and function. One of the most exciting advances in neuroimaging includes the capability of imaging of connections within and between regions (Friston, Frith et al. 1993; Biswal, Yetkin et al. 1995; Basser and Pierpaoli 1996; Conturo, Lori et al. 1999) and, more recently, how they are modified throughout development (Barnea-Goraly, Menon et al. 2005; Fair, Dosenbach et al. 2007; Fair, Cohen et al. 2008; Muetzel, Collins et al. 2008; Kelly, Di Martino et al. 2009). Neural connectivity is a term describing a complex, plastic network of structural and functional connections between brain regions during task-related activity and at rest. The current review is organized around the hypothesis that the pathophysiology of MDD involves altered development of connections within neural networks.

Models for the pathophysiology of depression are constantly evolving, but have consistently highlighted several interrelated "corticolimbic" brain circuits as central to the disorder (Figure 1): (1) **Hypothalamus and Pituitary:** Abnormalities in the hypothalamic-pituitary-adrenal axis, realized through overproduction of adrenocorticotropic hormone in the anterior pituitary, increased glucocorticoid release from the adrenal glands and subsequent damage to hippocampal neurons, has been a consistently implicated mechanism in depression (Sapolsky, Uno et al. 1990; Jacobs, van Praag et al. 2000). Hippocampal and pituitary volume changes in adult MDD recently withstood the rigors of a meta-analysis (Kempton, Salvador et al. 2011). (2) **Prefrontal Cortex (PFC):** Functional abnormalities in prefrontal regions, specifically subgenual and rostral "affective" anterior cingulate (ACC) regions, dorsolateral and orbitofrontal cortex (Videbech 2000; Pizzagalli, Oakes et al. 2004) have important implications for self-referential processing and normalization of mood state via interactions with striatal (caudate and putamen) and limbic nodes (Pizzagalli 2011). (3)**Amygdala:** The amygdala has structural and functional connections to the hippocampus, striatum and PFC. The amygdala evaluates the emotional significance of different kinds of stimuli, including those that might be threatening or rewarding and appears to bias perception toward a negative emotional valence in depression (Bellani, Baiano et al. 2011). As discussed below, amygdala volume and activation changes associated with MDD are inconsistent.

In this review we present the first comprehensive summary of existing neuroimaging research in child and adolescent depression. For the purposes of this review, we define childhood as occurring from infancy to prior to puberty and adolescence as the peri- and post-pubertal stage that ends prior to age eighteen. In the first three sections, we will review findings on regional differences from studies that examined the volume, function, and neurochemical makeup of specific regions in the brain. These regional findings provide the framework for the second wave of research that has examined changes at the level of networks or connectivity, covered in section four. This review also considers a number of moderating variables such as age, gender, psychiatric comorbidities and duration of illness. We will attempt to synthesize these factors into our overall understanding of pediatric MDD.

Throughout this review, important developmental distinctions uncovered through neuroimaging of children and adolescents will be highlighted. When data is available, we also review youth at risk for depression. By capturing both markers of disease susceptibility as well as threshold-level pathophysiology, this investigational approach allows for the possibility that MDD is a disorder with neural pathology evident early in development, perhaps before the onset of cognitive or behavioral symptoms. Depression has been conceived as a disorder with various symptom trajectories, including those that emerge in childhood, those that do not appear until adolescence and those that emerge in childhood but remit (Dekker, Ferdinand et al. 2007). Similarly, we propose an explanatory model that abnormal corticolimbic structural and functional connectivity observed in the neuroimaging studies reviewed here may also occur in parallel with distinct brain development trajectories. Furthermore, we model three possible trajectories of MDD defined by deviance from normal brain development over time (Figure 2): (1) Cases where genotype contributes to early pathophysiology that is worsened by environmental stressors and related gene expression changes ("Early Abnormal"); (2) Typical neural development early in life, but gradual deviance from this track with accumulating environmental adversity ("Gradual Abnormal"); and (3) Typical brain development through childhood, then an abrupt switch to atypical development in adolescence or adulthood ("Abrupt Abnormal"). Support for one or more of these models will be sought throughout this review of pediatric neuroimaging studies.

Methods

A literature search of the PUBMED and Ovid MEDLINE databases through June 2011 was carried out using permutations the following search words: depression, major depressive disorder, child, adolescent, pediatric, neuroimaging, magnetic resonance imaging, MRI, functional magnetic resonance imaging, fMRI, magnetic resonance spectroscopy, MRS, resting state functional connectivity, diffusion tensor imaging and DTI. In addition, relevant review articles were searched (Casey, Jones et al. 2008; Drevets, Price et al. 2008; Greicius 2008) and other publications were cross-referenced for any additional published articles. Papers that were not written in English, book chapters, conference abstracts, case studies and articles published in journals not indexed on PUBMED or Ovid MEDLINE were not reviewed. Computerized tomography (CT) and single photon emission tomography (SPECT) studies were omitted given their lack of utility in psychiatric research in children and adolescence due to radiation exposure.

Results: Neuroimaging Findings in Child and Adolescent Major Depression

I. Volumetric Studies

The majority of brain imaging results that are available from pediatric depression studies come from studies reporting differences in the volumes of specific areas of interest. Volumetric MRI of brain structures involves either tracing brain regions to quantify a calculable volume for group comparison, or makes use of a newer technique, voxel based morphometry (VBM). VBM involves registration of the image to a standardized template, which normalizes volume across subjects (Ashburner and Friston 2000). Normalized brain images are then spatially smoothed to reduce measurement noise. Finally, parametric statistics are typically applied only to gray matter volume across the entire brain, allowing for between-group comparisons. Volumetric studies have served a critical role in identifying the key regions that are implicated in pediatric depression. These results have provided the scaffolding for more recent connectivity-focused approaches by identifying the critical nodes of neural networks implicated in depression. Volumetric neuroimaging reviews in depressed adults largely converge on findings of decreased volume in widespread cortical regions (Fitzgerald, Oxley et al. 2006; Koenigs and Grafman 2009), although there is evidence of acute enlargement of subcortical regions, such as the amygdala (Frodl, Meisenzahl et al. 2003; van Eijndhoven, van Wingen et al. 2009), during depressive illness. Here we take the view that early in the course of depression, pathology may be represented by a volume increase or decrease. Regional volume increases, as have been observed in schizophrenia (Spoletini, Piras et al. 2011), fibromyalgia (Schmidt-Wilcke, Luerding et al. 2007) and autism (Kim, Lyoo et al. 2010), suggest a compensatory effort. Atrophy, or volumetric decreases, have been seen more commonly across many psychiatric and neurodegenerative disorders, including MDD (Kanner 2004) and likely indicate hypofunctioning neural tissue. Volume states may also be impacted by treatments, thus drug treatment status will be noted for each study.

Cortical Regions—Table 1 summarizes volumetric MRI findings in children and adolescents. In the first published study involving MRI and youth with a primary diagnosis of MDD, Steingard and colleagues found that children hospitalized with depressive disorders had smaller frontal lobe and larger lateral ventricular volume than hospitalized psychiatric controls when controlling for total cerebral volume (Steingard, Renshaw et al. 1996). In a follow-up study, depressed, largely psychotropic naïve adolescents had significantly smaller whole brain volumes when compared to age-, race-, and gender-matched healthy control subjects (Steingard, Renshaw et al. 2002). When controlling for whole brain volumes, frontal white matter volumes were significantly smaller, while frontal grey matter volumes were significantly larger in the MDD group, compared to controls (Steingard, Renshaw et al. 2002).

As have been observed in adults with MDD (Price and Drevets 2010), many studies in pediatric MDD have identified structural abnormalities in frontal regions including the prefrontal cortex (PFC), orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). In an early study, Nolan and colleagues (Nolan, Moore et al. 2002) imaged the subgenual prefrontal cortex (PFC) of psychotropic naïve depressed children. Among depressed psychotropic naïve subjects, those with non-familial (e.g. lacking first degree relatives) MDD had significantly larger left-, but not right-, sided subgenual prefrontal cortical volumes than subjects with familial MDD and healthy case-matched controls (Nolan, Moore et al. 2002). In contrast, Drevets and colleagues found *smaller* left sided prefrontal total grey matter volumes in depressed adults (Drevets, Price et al. 1997). Although the studied areas were not identical, authors hypothesized that the discrepancy in the direction of the group difference may indicate that decreased PFC volumes are the result of duration of illness, illness severity, and genetic loading, while increased PFC volumes in new-onset youth without a family history of MDD could indicate “abnormal PFC maturation.” As is representative of MDD in the general population, the Nolan sample contained a majority of subjects with comorbid Axis I disorders. In particular, patients with oppositional defiant disorder (ODD) disproportionately populated the non-familial depression group, and the authors acknowledged there could be a distinct subtype of MDD with comorbid ODD that is particularly prone to decreased PFC volume. Disruptive behavior disorders such as ODD have been noted in longitudinal studies to increase risk for MDD and may be thought of as prodromal or contributory to MDD (Burke, Hipwell et al. 2010; Bussing, Mason et al. 2010; Mazza, Fleming et al. 2010).

Based on prior research showing reduced volume of the orbitofrontal cortex (OFC) in adults with MDD, Chen and colleagues (2008) examined OFC volumes in medication naïve adolescents with MDD and controls. Authors reported no significant differences in total OFC volume or OFC gray matter volume, but exploratory analyses revealed that patients had larger total and gray matter volumes of the right lateral subregion of the OFC. It was suggested that the findings of decreased volume in OFC found in adult MDD may be related to neural loss that occurs later in life (Chen, Rosenberg et al. 2008).

Abnormalities in the rostral anterior cingulate cortex (rACC) represent a candidate biomarker for depression from adult neuroimaging studies (Drevets, Price et al. 1997; Mayberg, Brannan et al. 1997) as well as from post-mortem neuropathology studies (Chana, Landau et al. 2003). A caveat worth noting is the difficulty in characterizing this morphologically complex region using MRI. This challenge may be reflected in the variable findings between studies and the small number of reports for this region. A study of healthy children revealed that in boys, rACC volume correlated negatively with depression symptoms, especially among boys with a family history of depression, and when the sample was divided based on severity of depression symptoms, boys with depressive symptoms had significantly lower rACC volumes than boys without depressive symptoms (Boes, McCormick et al. 2008). These findings were not present in girls (Boes, McCormick et al. 2008). In a more recent study of adolescents with co-morbid MDD and borderline personality disorder (BPD) a group- by- rACC volume by- matter type (gray, white) interaction was reported, in which the patient group had smaller gray but not white matter rACC volumes.(Goodman, Hazlett et al. 2010). RACC volume in this study was correlated with suicide attempts and BPD symptom severity, but not with depression symptom severity (Goodman, Hazlett et al. 2010). In sum, PFC global and subregion analyses are preliminary, but do indicate a trend toward decreased volumes in children with MDD, which appear to be influenced by psychiatric comorbidity.

Cortical Thickness—Recent explorations of regional cortical thickness have included youth at risk and afflicted with depression. Peterson et al (2009) measured cortical thickness in 18–61 year olds who were either high or low risk for the development of depression. Statistically significant cortical thinning was observed in the high-risk group in the subgenual, anterior and posterior cingulate and medial orbitofrontal cortex of the right hemisphere only (Peterson, Warner et al. 2009). Findings were similar between adults and children and did not change when models co-varied for the presence of lifetime depression or anxiety disorders. Cortical thinning correlated with measures of current symptom severity, inattention, and visual memory for social and emotional stimuli (Peterson, Warner et al. 2009) Cortical thickness was also found to be abnormal in the right and left sides of the brain in psychotropic drug-naive depressed children and adolescents compared to controls (Fallucca, MacMaster et al. 2011). Specifically,the right pericalcarine gyrus, postcentral gyrus and superior parietal gyrus and left supramarginal gyrus were significantly thinner in participants with MDD than in matched healthy controls. The right and left temporal poles were thicker in the MDD group. The authors suggest that parietal and supramarginal regions were unexpected and underscore the need to explore beyond the typically described frontal-limbic mood regulating circuit. Thus two large studies of well-characterized high risk and depressed youth converge on a large number of abnormally thinned cortical regions that may precipitate and perpetuate the early phases of depressive illness.

Amygdala and Hippocampus—The amygdala and hippocampus are limbic regions involved in the regulation and memory of emotion and are reliably implicated in the etiology and maintenance of depressive symptoms. In adults with a first episode of MDD, the left and right amygdala were enlarged compared to healthy controls (Frodl, Meisenzahl et al. 2003), although amygdala volumes have been found to be normal, enlarged, and decreased in chronically depressed adults (Sheline, Gado et al. 1998; Bremner, Narayan et al. 2000; Mervaala, Fohr et al. 2000). A review of adult literature has suggested that amygdala volume is likely influenced by medication exposure (Hamilton, Siemer et al. 2008). Reviews of imaging studies of adults with MDD have demonstrated a consensus of reduced hippocampal volumes, particularly in elderly and chronic samples (Savitz and Drevets 2009). Volume reduction of the hippocampus has been associated with duration of depression in adults with MDD (Bremner, Narayan et al. 2000; Mervaala, Fohr et al. 2000; Sheline 2000; MacQueen, Campbell et al. 2003).

In the first volumetric evaluation of the amygdala and hippocampus in pediatric depression, comparison of psychotropic-naïve depressed children and adolescents to healthy controls matched for age, sex, weight, and height revealed no group differences in amygdala or hippocampal volumes when these were measured independently, controlling for age and intracranial volume. A comparison of amygdala/hippocampus ratios revealed that depressed subjects had larger left and right amygdala, relative to hippocampus, volumes (MacMillan, Szeszko et al. 2003). Among depressed participants, amygdala/hippocampus volume ratios were associated with anxiety severity but not measures of depressive severity or duration of illness. Re-analysis of these data showed that volumetric alterations were more prominent in depressed individuals with a family history of one first-degree relative with MDD, compared to those with non-familial MDD (MacMaster, Mirza et al. 2008). Despite a high rate of comorbid anxiety disorders, anxiety did not correlate with any regional volume differences. As a caveat to these studies, the authors noted some difficulty in identifying a boundary separating the amygdala and the hippocampus in some of their subjects (MacMillan, Szeszko et al. 2003).

In early-onset depressed adolescents, left hippocampal volumes were reduced by 17% compared to healthy comparisons, and smaller left hippocampal volumes (trend on the right) were more prominent in males than females (MacMaster and Kusumakar 2004). Also, similar to findings from geriatric MDD (Steffens, Byrum et al. 2000), a decreased correlation between age of onset of depression and hippocampal volume was noted (MacMaster and Kusumakar 2004). The authors noted that, unlike studies in adult depression, hippocampal size was positively correlated with the duration of illness. The authors speculate that this positive relationship may be a developmental course aimed at neural recovery. Trait anxiety, which has been linked to hippocampal volume, was not controlled for in this study. The authors reported that no subjects had comorbid anxiety disorders, which makes this sample unusual given high rates of co-morbid anxiety in pediatric MDD. This study did not report findings regarding the amygdala.

In a predominantly female sample, Rosso et al reported smaller amygdala volumes, but no hippocampal volume differences, in recent-onset (mean of 2 years since illness onset) depressed, medicated pediatric patients compared to controls (Rosso, Cintron et al. 2005). Neither depression severity nor duration of illness predicted amygdala or hippocampal volumes. However, age at onset was significantly associated with right hippocampal volumes. Subgroup analyses did not reveal any group effects for family history status, psychotropic drug use, or comorbid DSM-IV Axis I diagnoses, although the authors note that the power to detect these associations was limited by the reduced variability of the recent-onset illness sample.

Although smaller hippocampal volumes were found in depressed pediatric patients with familial MDD compared to healthy controls, no group volumetric differences were observed for the amygdala (MacMaster, Mirza et al. 2008). These findings contrast with evidence that amygdala volumes were increased in a first episode of MDD in adults (Frodl, Meisenzahl et al. 2003). In a separate study, a mixed sample of psychotropic naïve and psychotropically treated depressed pediatric subjects had smaller left hippocampal volumes, but no differences in amygdala volumes, compared to controls (Caetano, Fonseca et al. 2007). Within this MDD group, there was a trend toward smaller amygdala volumes among subjects with MDD with anxiety versus those without co-morbid anxiety disorders. Authors suggested that difficulties in reliably measuring the amygdala means that large samples are required to produce robust differences in pediatric depression samples (MacMaster, Mirza et al. 2008). In addition, an inverse correlation of amygdala volume with dose and duration of SSRI use (albeit in pediatric OCD), suggests that medication status may play a role with amygdala volume in MDD (Szeszko, MacMillan et al. 2004).

Two recent studies have contributed additional findings supporting reduced volume of hippocampus in pediatric depression. Rao et al. examined adolescents with MDD, adolescents at high familial risk for MDD and healthy low risk controls (Rao, Chen et al.

2010). The authors reported that: (1) both the depressed and the high-risk group had smaller left and right hippocampal volumes than the control group; (2) higher levels of early-life adversity were associated with smaller hippocampal volumes; and (3) small hippocampal volumes partially mediated the effect of early-life adversity on depression during longitudinal follow-up (Rao, Chen et al. 2010). These findings were comparable to another recent study that included adolescents at high familial risk for depression, which found smaller volumes in the left hippocampus and lower gray matter density in bilateral hippocampal clusters in high-risk compared to low-risk participants (Chen, Hamilton et al. 2010). Thus, consistent with adult neuroimaging findings, amygdala and hippocampal volumes appear, overall, to be smaller in MDD and high-risk subjects compared to controls. Preliminarily, smaller volumes were associated with early-life adversity, family history of depression, onset during adolescence and co-morbid anxiety in pedatric MDD samples.

Pituitary—Because the stress system mediated by the hypothalamic-pituitary-adrenal axis has been consistently implicated in adult depression, the pituitary has also been examined as a region of interest in volumetric studies. MacMaster and Kusumakar were the first to image pituitary volumes in depressed adolescents (MacMaster and Kusumakar 2004). They found an increase in pituitary volume among a mainly unmedicated depressed cohort compared to age- and sex-matched healthy controls. Healthy subjects confirmed previous findings that pituitary volumes normatively increase with pubertal age and that females have larger volumes than age-matched males, possibly due to an earlier pituitary growth spurt among girls (Takano, Utsunomiya et al. 1999). Interestingly, these age and gender differences were not present in depressed subjects, perhaps, as the authors suggest, because normal subtleties of pituitary development are overwhelmed by physiological changes that accompany depression (MacMaster and Kusumakar 2004).

In a report from 2006, MacMaster and colleagues again found larger pituitary volumes in psychotropic naïve pediatric and adolescent males with MDD compared to controls (MacMaster, Russell et al. 2006). However, no group differences were seen in girls with MDD compared to controls. Gender differences were absent among the depressed children. Depressed boys without a family history of MDD had a larger pituitary volume than controls and had a trend-level increase over boys with familial MDD. The authors suggested that these results point to a central neurobiological deficit, particularly among boys with nonfamilial MDD. Of note, the boys with the largest pituitary volumes were also diagnosed with ODD. Illness duration and age of onset did not correlate with pituitary volume, suggesting that pituitary volume change may be an early marker of depressive illness. MacMaster et al. (2006) also reported pituitary abnormalities (*decreased* volumes) seen only in boys with obsessive compulsive disorder, suggesting that the pituitary may be a gender-specific marker for early life mood and anxiety disorders.

Striatum—In the only study of striatal volumes in pediatric depression depressed, medication-naïve subjects had significantly smaller right striatal and right caudate volumes compared to demographically matched healthy subjects (Matsuo, Rosenberg et al. 2008). Left caudate volumes were inversely correlated with depression severity and age was inversely correlated with left and right putamen volumes in MDD patients, but not in the healthy subjects (Matsuo, Rosenberg et al. 2008). The authors noted that their sample had high rates (67%) of comorbid anxiety disorders and ADHD, which have been shown to affect caudate and putamen volumes.

Structural Volumes and Environmental Interactions—In a novel approach relating parenting behavior to depressive symptoms, Yap and colleagues explored the relationship of depressive symptoms across multiple brain regions in non-depressed 11–13 year olds (Yap, Whittle et al. 2008). They found that boys with smaller right amygdala volumes reported more depressive symptoms, while hippocampal and ACC volumes were not related to the reported level of depressive symptoms. Notably, the frequency of observed maternal aggressive behaviors during an observed parent-adolescent interaction moderated the associations between both the amygdala and ACC volumes and adolescent depressive symptoms. When low levels of maternal aggression was observed, boys with larger right amygdala, girls with smaller bilateral amygdala, and both boys and girls with smaller left paralimbic ACC volumes reported fewer symptoms. This work is the first in the pediatric depression neuroimaging literature to highlight the notion that certain neuroanatomic features might be associated with depressive symptomatology only in the context of particular environmental circumstances, in this case high parentally expressed negative emotion. Similar studies in pediatric subjects with MDD are needed.

In conclusion, volumetric abnormalities have been observed in key corticolimic brain regions in pediatric MDD samples, and these results have prompted further investigations into these networks. Important moderating variables have been noted in these studies including symptom severity, family history, history of adversity, age of onset, duration of illness, medication exposure, co-morbid conditions, gender and age. These moderating variables have not been systematically addressed in the volumetric literature and their impact on neuroimaging findings is uncertain. Most findings presented above were completed with small sample sizes and require replication that accounts for psychotropic status and comorbid psychiatric conditions. The exceptions are decreased hippocampal (MacMaster and Kusumakar 2004; Caetano, Fonseca et al. 2007; MacMaster, Mirza et al. 2008; Chen, Hamilton et al. 2010; Rao, Chen et al. 2010) and increased pituitary (MacMaster and Kusumakar, 2004; MacMaster et al., 2006) volumes, which were replicated in at least two independent samples. The significance of how volumetric MRI findings relate to functionality remain unclear. It does appear that volumetric abnormalities are present in at least a subset of patients early in life, prior to multiple treatment and illness episodes, lending support to the “Early Abnormal” model of brain development, as proposed in Figure 2. Longitudinal data will be required to confirm this trajectory. Despite these limitations, volumetric results have served an important role in the identification of key frontal-striatal-limbic regions implicated in pediatric depression and have contributed to a systems model for future studies of brain circuitry.

II. Regional Brain Function

Functional magnetic resonance imaging (fMRI) indirectly quantifies neural activity during rest or while a subject is completing a task by measuring the blood oxygen level dependent (BOLD) signal. Traditional fMRI experiments measure increases or decreases in BOLD signal during a specific task in comparison to baseline. Because we discuss the application of resting state fMRI to examine brain connectivity in a subsequent section, here we refer to traditional fMRI experiments as “task-based fMRI” studies.

Task-based fMRI has been widely used in psychiatric disorders, including adult depression. Most task-based fMRI studies on depressed subjects have attempted to capture maladaptive aspects of emotional regulation, a core feature of all affective disorders. The paradigms studied in pediatric MDD include facial recognition, cognitive control and reward processing and are summarized in Table 2.

Facial Recognition—The most widely studied task-based paradigm in child and adolescent depression fMRI research has been the measurement of the neural response to viewing facial expressions. Neuroimaging work in healthy adults has shown that facial recognition tasks with fearful faces are probes for amygdala activity (Fusar-Poli, Placentino et al. 2009). In healthy adolescents, bilateral amygdala activation was greater when fearful faces were shown, compared to neutral expressions (Baird, Gruber et al. 1999). Healthy children, on the other hand, had less amygdala activation with fearful than neutral face probes (Baird, Gruber et al. 1999). These disparate findings preliminarily suggest an age-related shift toward the amygdala's sensitivity to fear in typically developing children.

Adults with MDD have generally shown amygdala hyperactivation on fMRI tasks of facial recognition (Sheline, Barch et al. 2001; Whalen, Shin et al. 2002; Fu, Williams et al. 2004). The first use of the facial recognition paradigm in depressed youth occurred in 2001 when Thomas and colleagues compared girls with MDD to anxious and healthy girls (Thomas, Drevets et al. 2001). They reported a blunted amygdala response in the 5 girls with MDD compared to controls, while anxious subjects demonstrated an exaggerated amygdala response, when shown images of fearful faces. This finding of a blunted response in pediatric MDD suggests a developmental difference, but was collected from a small sample of females and had not yet been replicated. Utilizing a "subsequent memory paradigm," Roberson-Nay and colleagues (Roberson-Nay, McClure et al. 2006) also explored facial recognition in adolescents with MDD, anxiety, and controls. In this study, the authors attempted to separate memory function from pure facial encoding, thus expanding on the work of Thomas et al (2001). Consistent with findings in adults, depressed adolescents had heightened left amygdala activation during successful encoding of images of emotional expressions (Roberson-Nay, McClure et al. 2006). These depressed subjects had poorer memory of faces than controls or anxious subjects, and it was only when faces were successfully remembered that amygdala hyperactivity was observed.

More recently, Monk and colleagues examined children and adolescents at high-versus low-familial risk for depression and examined face processing during passive viewing of emotion faces and also during constrained viewing (i.e., asked to rate specific aspects of the face during viewing) (Monk, Klein et al. 2008). This study revealed that high-risk participants showed greater amygdala and nucleus accumbens activity during passive fear face processing, and lower nucleus accumbens activation during passive happy face processing. No group differences were noted during constrained face viewing, but exploratory analyses revealed that constraining attention was associated with higher medial PFC in the high risk than the low-risk group (Monk, Klein et al. 2008), consistent with amygdala dampening previously observed during cognitive tasks (Kober, Barrett et al. 2008).

In summary, while studies in adults have demonstrated elevated amygdala activation while processing fear, this finding has been replicated in some but not all studies of children and adolescents with depression as well as in youth at elevated risk for depression. Sophistication in these techniques, such as inclusion of attention constraints, examination of multiple emotions, and examination of multiple regions of the brain, have allowed for a more enriched understanding of how emotion processing is abnormal in youth with or at risk for depression.

Cognitive Control Tasks—In an attention-focused battery, medication-naıve adolescents with a first-episode of MDD and healthy adolescents were compared on tasks involving selective attention (Simon task), attentional switching (Switch task), motor response inhibition and error detection (Stop task) tasks (Halari, Simic et al. 2009). In all three tasks, the MDD group demonstrated a lower level of activation in task-relevant regions including right dorsolateral PFC, inferior PFC and ACC compared to controls. Additional areas of relatively reduced activation were in the parietal lobes during the Stop and Switch tasks, putamen, insula and temporal lobes during the Switch task and precuneus during the Simon task. This study presented the first evidence that medication-naıve adolescents with MDD can be characterized by brain activation changes similar to those of depressed adults during tasks of attention and performance monitoring. The authors hypothesize that their findings suggest an early pathogenesis of these functional abnormalities in the course of MDD (Halari, Simic et al. 2009).

The emotional variant of the Stroop task has been used by researchers to examine the integration of emotional and cognitive information (Whalen, Bush et al. 1998). In a study of high-risk adolescents and young, Mannie and colleagues (2008) reported that healthy youth showed significant activation in pregenual ACC to both positive and negative words during the emotional Stroop task, which was absent in the high-risk group (Mannie, Norbury et al. 2008). These findings suggested a deficit in the risk group for integrating emotionally valenced stimuli, potentially representing a risk marker for MDD.

In sum, such neural abnormalities as reduced activation in key frontal and cingulate areas during cognitive control tasks are found in both adults and children with MDD, and a similar pattern is also observed in high-risk youth prior to onset of depression.

Reward Processing—Depression has been postulated to have underlying disordered reward processing, including reward seeking, motivation, and reduced enjoyment (Elliott, Sahakian et al. 1998), suggesting that pathways traditionally associated with reward through the striatum, amygdala, and orbitofrontal cortex are implicated. Functional neuroimaging in depressed adults has found abnormal activation in these regions, with decreased ventral striatum activation to pleasant visual stimuli (Lawrence, Williams et al. 2004) and anhedonia associated with lower amygdala and ventral striatum activation (Keedwell, Andrew et al. 2005), although the mechanism of the dysfunction remains unclear. Reward processing studies in depressed children and adolescents have shown that depressed boys inadequately discriminated between low- and high-magnitude rewards under high-probability conditions and that impaired reward processing predicted depressive symptoms one year later (Forbes, Shaw et al. 2007). The same group also explored reward decision-making and outcome in a largely female sample of children and adolescents with MDD and other psychiatric co-morbidities (Forbes, Christopher May et al. 2006). In the decision phase of the scan, depressed subjects showed blunted responses in the ACC, caudate, and OFC, which the authors interpreted as a decreased emotional response to a reward. During the outcome phase, those with depression had diminished responses in the ACC, caudate, and OFC, but hyperactivation in the amygdala. The authors extrapolated that these data point to difficulty in depressed youth with decision-making, monitoring error, and motivation (Forbes, Christopher May et al. 2006).

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In a more recent exploration, children and adolescents with and without MDD completed an fMRI task involving monetary reward and a self-reported rating of affect in the subjects' real world environments through a four-day cell-phone-based assessment (Forbes, Hariri et al. 2009). Subjects with MDD exhibited less striatal response than control subjects during reward anticipation and reward outcome, but more response in dorsolateral and medial PFC relative to controls. Diminished activation in the caudate was correlated with lower subjective positive affect in natural environments, particularly within the depressed group. The authors concluded that brain response to monetary reward is related to actual affective experience (Forbes, Hariri et al. 2009).

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Finally, a recent study of young girls at high and low familial risk for MDD was conducted by Gotlib and colleagues, who reported group differences from reward and punishment task (Gotlib, Hamilton et al. 2010). This study found that while anticipating gains, the high-risk group showed less activation in the right insula. However, when receiving punishment, the high-risk participants showed greater activation in dorsal ACC than low-risk participants.

During punishment, the low-risk group showed greater activity in caudate and putamen than the high-risk group (Gotlib, Hamilton et al. 2010).

Task-based functional neuroimaging studies have greatly enhanced our understanding of how brain functioning during specific tasks is altered in youth with depression and in youth at risk for depression. From the three overall thematic paradigms reviewed here—face processing, cognitive control, and reward processing—results converge on hypo- and hyperactivation impairments in frontal, limbic and striatal regions implicated in various aspects of emotion processing and regulation. Such studies have confirmed the importance of specific regions that had been identified in structural studies (e.g. amygdala, PFC, ACC), substantiated theories regarding the role of hypothesized regions (e.g. nucleus accumbens playing a role in reward processing) and identified new areas of interest (e.g. insula, caudate) that provide impetus for further study of neural networks in depression. Considered together, these studies that have identified neural correlates of MDD that are analogous to findings in adults support the “Early Abnormal” developmental trajectory model.

III. Regional Neurochemistry: Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (MRS) has been the most commonly utilized method to study neurochemical underpinnings of MDD in human subjects. MRS noninvasively measures a number of compounds present in the human brain that serve as markers for neuronal integrity and degeneration, neurotransmitter levels, glial cells, and brain energy stores, as detailed in Table 3. MRS data has served to identify the important areas that are neurochemically abnormal in depression, again contributing to a network-level model that can be assessed with other methods. Pediatric studies are summarized in Table 4.

Cortex—MRS findings in pediatric major depression have been reviewed in at least three recent publications (Yildiz-Yesiloglu and Ankerst 2006; Gabbay 2008). The first applications of proton MRS to pediatric subjects with MDD reported that medial thalamic choline concentrations did not differ between psychotropic naïve pediatric patients with MDD and healthy controls (Smith, Russell et al. 2003). Another group found lower left amygdalar choline/Cr ratios in a very small cohort of depressed 14–18-year-olds compared to controls (Kusumakar, MacMaster et al. 2001). They also noted a negative trend relating depression severity and choline/Cr ratios in the left amygdala. Finally, relative to comparison subjects, adolescents with severe MDD had significantly elevated concentrations of choline and creatine in the left caudate (Gabbay, Hess et al. 2007). No other neurochemical differences were observed between the groups. The authors interpreted that these findings reflect accelerated membrane turnover and impaired metabolism and are consistent with prior imaging reports of lateralized abnormalities in the caudate in adult depression.

MRS studies focusing on cortical regions have implicated numerous neurochemical abnormalities in depression. In the first pediatric exploration of the cortex, Steingard and colleagues reported higher orbitofrontal cortex choline/creatine and choline/N-acetylaspartate ratios among depressed, psychotropically treated adolescents compared to controls (Steingard, Yurgelun-Todd et al. 2000). Measures in the left dorsolateral PFC of treatment naïve subjects with MDD had higher concentrations of choline than healthy controls (Farchione, Moore et al. 2002). No group differences were found when NAA or Cr were measured, nor did group choline levels differ significantly in the right dorsolateral prefrontal cortex. Also in the dorsolateral PFC, Caetano et al. found significantly lower levels of choline containing compounds and higher levels of myoinositol levels in their sample of depressed, not treatment naïve, children and adolescents compared to demographically matched controls (Caetano, Fonseca et al. 2005). There was an inverse correlation between glutamate levels and duration of illness and number of episodes. The authors speculate that lower choline-containing compounds may represent lower membrane turnover and smaller numbers of glial cells, while myoinositol levels point to abnormalities in the intracellular second messenger system (Caetano, Fonseca et al. 2005). In a more recent MRS study exploring the medial temporal cortex (MTC), eleven MDD case-control pairs showed lower N-acetyl-aspartate (NAA) in the left MTC, possibly reflecting reduced neuronal viability in that region (MacMaster, Moore et al. 2008).

Glutamatergic concentrations were significantly lower in psychotropic naïve MDD patients versus age- and gender-matched controls in the ACC and were associated with severity of functional impairment (Mirza, Tang et al. 2004), while glutamatergic concentrations in the occipital cortex did not differ between controls and depressed subjects (Mirza et al, 2004). In a similar study, glutamatergic concentrations were significantly lower in the anterior cingulate cortex of psychotropic naïve children with MDD and OCD compared to matched controls (Rosenberg, Mirza et al. 2004). ACC glutamatergic concentrations did not differentiate patients with MDD and those with OCD, and no group differences were found for NAA, Cr, or Cho (Rosenberg, Mirza et al 2004). In a newer analysis of glutmate/ glutamine compounds from the above studies of the ACC, Rosenberg and colleagues (2005) confirmed reduced ACC glutamate in psychotropic naïve MDD versus case-matched control subjects, but did not find group differences for glutamine levels (Rosenberg, Macmaster et al. 2005). Again, no significant differences were found for occipital cortex glutamate or glutamine. The authors explained that MRS glutamate levels are dependent on intact neurons and glia (Gallo and Ghiani 2000), suggesting that lower glutamate levels may represent abnormal neuronal density and metabolism, likely synonymous with altered neuronal connectivity. Olvera and colleagues (2010) found lower NAA in adolescents with depression than healthy controls in the right ACC and right medial PFC (Olvera, Caetano et al. 2010). The authors suggested their findings represent decreased neuronal integrity in these areas.

In summary, a growing number of MRS studies have found abnormalities in brain metabolites in cortical and subcortical regions in depressed children and adolescents that are suggestive of impaired cellular health in those areas. As with volumetric and functional MRI studies, small numbers of subjects were used and not all studies controlled for psychotropic use and other psychiatric comorbidities. These early correlates add to structural and fMRI findings implicating regions within corticolimbic circuitry in the pathophysiology of MDD. Although longitudinal neuroimaging data are not available, these cross-sectional findings also preliminarily support the “Early Abnormal” developmental trajectory.

IV. Network Based Approaches: Connectivity

The study of connectivity within brain networks in children and adolescents with MDD holds considerable promise for understanding the neurodevelopmental mechanisms of pediatric MDD. Refinement of neural connections is known to continue through childhood and adolescence during normative development (Fair, Dosenbach et al. 2007; Casey, Jones et al. 2008; Kelly, Di Martino et al. 2008). A clear understanding of how these processes go awry in children and adolescents with depression will allow a deeper understanding of the pathophysiology at a systems level. Here we discuss two imaging methods to examine brain connectivity: functional connectivity using fMRI and structural connectivity using diffusion tensor imaging.

Functional Connectivity—Functional resting state imaging measures spontaneous fluctuations in BOLD signal while the subject lies in the MRI scanner at rest (Biswal, Yetkin et al. 1995; Fox and Raichle 2007). The patterns of fluctuations are examined among different brain regions and strong correlations between these interregional temporal patterns are thought to represent "functional connectivity." Since the discovery that patterns of functional connectivity have been shown to map on to known anatomical connections (Biswal, Yetkin et al. 1995), this method has been used to examine how functional connectivity differs in many psychiatric conditions (Greicius 2008).

A number of studies have now reported results using resting state functional connectivity MRI in adults with MDD (Anand, Li et al. 2005; Anand, Li et al. 2005; Anand, Li et al. 2007; Greicius, Flores et al. 2007; Yao, Wang et al. 2009; Hamilton, Chen et al. 2010; Liu, Xu et al. 2010; Sheline, Price et al. 2010; Veer, Beckmann et al. 2010). Using a region of interest approach, Anand and colleagues reported lower resting state corticolimbic connectivity compared to controls (Anand, Li et al. 2005), with movement toward normalization after antidepressant treatment (Anand, Li et al. 2005; Anand, Li et al. 2007). Another region-of interest study examined three networks (cognitive control, default mode, and an affective network), and reported higher connectivity for depressed subjects in bilateral dorsal medial PFC for all 3 networks (Sheline, Price et al, 2010). Greicius and colleagues (2007) used an independent component analysis (ICA) to isolate the default mode network (DMN), and reported that in adults with depression, the DMN included more connections to subgenual ACC and thalamus than controls (Greicius, Flores et al. 2007).

The first study conducted using resting state fMRI in youth examined functional connectivity in adolescents with MDD and healthy controls (Cullen, Gee et al. 2009). Using a seed-based connectivity analysis, adolescents with MDD had decreased functional connectivity in a subgenual ACC-based neural network that included the supragenual ACC, the right medial frontal cortex, the left inferior and superior frontal cortex, superior temporal gyrus and the insular cortex. These preliminary data suggest that MDD in adolescence is associated with abnormal connectivity within neural circuits that mediate emotion processing, although future research in larger, unmedicated samples will be necessary to confirm this finding.

More recently, a study of children with a history of preschool-onset MDD also demonstrated abnormal subgenual ACC functional connectivity. However, the patient group exhibited greater sgACC connectivity with thalamic and parietal regions than controls, and less connectivity than controls with cognitive control regions (Gaffrey, Luby et al. 2010). A significant correlation between dysregulated emotional behavior and connectivity of the sgACC and dorsal medial prefrontal cortex was also found. Given the ease of administration relative to task-based fMRI in children and the information provided regarding circuitry, this technique holds promise for advancing our current understanding of pediatric MDD.

Diffusion Tensor Imaging—Diffusion tensor imaging (DTI) is a technique that quantifies water molecule motion in the brain. Myelinated fibers restrict the diffusion of water to the axis of the fiber bundle, resulting in visualization of white matter tracts. Beyond conventional MRI, DTI can provide additional information on axonal integrity and bundle coherence, thus estimating the structural efficiency of neural pathways. The metrics commonly used in DTI studies include fractional anisotropy (FA) and mean diffusivity (MD). High axonal integrity and resultant limitation of water diffusion in the white matter would be associated with high FA values and low MD values. A large number of studies from the early 2000s in healthy subjects showed a general increase in FA and decrease in MD with normal maturation in childhood, adolescence and early adulthood (Cascio, Gerig et al. 2007). DTI has been studied extensively in adult MDD, with findings largely converging on lower FA in limbic, thalamic and prefrontal projection fibers (Sexton, Mackay et al. 2009).

In the first study to examine white matter using DTI in pediatric depression, Cullen et al. (2010) used probabilistic tractography to delineate the connection between subgenual ACC and bilateral amygdala and reported patients with depression had lower FA on the right than healthy controls (Cullen, Klimes-Dougan et al. 2010). This study also used a voxel-wise approach to look across the brain, and found 10 regions with lower FA in the MDD group, in tracts including the left and right uncinate fasciculi, the left and right inferior fronto-occipital fasciculi, left anterior cingulum, and left superior longitudinal fasciculus. No clusters with significantly higher FA were seen in the depressed group compared to the control group.

Finally, a DTI study from at-risk adolescents has recently been published (Huang, Fan et al. 2011). This voxel-wise study reported that adolescents at risk for depression had lower FA in left cingulum, splenium of corpus callosum, superior longitudinal fasciculus, uncinate, and interior fronto-occipital fasciculus compared to controls. Given the overlapping findings with the adolescent MDD study by Cullen and colleagues, this data supports the hypothesis that white matter deficits develop early in life, and are not a result of chronic depression or its treatment.

While the number of studies utilizing methods capable of assessing connectivity is quite small, there is evidence that connectivity-based disruptions are associated with pediatric cases of MDD. Hypotheses regarding the developmental course of these abnormal brain networks should be addressed in future longitudinal MDD studies powered to report on covariates such as age of onset, treatment history, comorbidity and family history.

Genetic Imaging—When utilized with genetic research, neuroimaging studies complement behavioral association by localizing gene effects within neural systems and circuits. Hariri and colleagues outline converging evidence from genetics and neuroimaging in work relating 5-HTTLPR polymorphisms and amygdala and corticolimbic circuitry, noting that developmental effects are largely undiscovered (Hariri, Drabant et al. 2006). Such theories have obvious implications in juvenile populations given the tremendous impact of early life environmental stress. The ability of imaging and genetics to marry these effects in individual studies offers promise in discerning relative contributions and interactions.

In a recent study looking at the impact of 5-HTTLPR on processing of sad faces in healthy children, Fortier et al (2010) reported that children homozygous for the short allele (S) showed greater activation than those homozygous for the long allele (L) during the sad condition (relative to the neutral condition) in bilateral putamen, bilateral caudate nucleus, and right ACC. No brain region was significantly more activated in the L group than in the S group (Fortier, Noreau et al. 2010).

A study on the effects of a genetic polymorphism on brain structure and function in males (n=50; ages 10–12 years) is among the first published reports of psychiatric genetic imaging in youth, although it was also conducted entirely on healthy controls (Mechelli, Tognin et al. 2009). The catechol-*O*-methyltransferase (COMT) valine (val) 158 methionine (met; val158met) allele has been shown to moderate predisposition to mood disorders and has been associated with gray matter volume in the left hippocampal head in depressed adults (Cerasa, Gioia et al. 2008). In this report, the met158 allele was also positively associated with gray matter volume in the left hippocampal head, where genotype accounted for 59% of inter-individual variance in hippocampal grey matter volume (Mechelli, Tognin et al. 2009). In addition, the met158 allele was positively associated with right parahippocampal gyrus activation to fearful expressions, where genotype accounted for only 14% of the variance in this region. Surprisingly, there was no effect of COMT genotype on amygdala activation or prefrontal cortex grey matter volume, as has been seen in adults.

A recent study examined the effect of a polymorphism of the human brain derived neurotrophic factor (BDNF) gene (Val66Met) on amygdala-hippocampal responses to emotional stimuli in adolescents with anxiety disorders and/or MDD and in healthy adolescents (Lau, Goldman et al. 2010). The authors reported greater activations in patients than healthy adolescents, and that these hyperactivations were modulated by BDNF genotype: Met-carriers showed greater neural responses of emotional faces than Val/Val homozygotes in patients only (Lau, Goldman et al. 2010).

These early studies demonstrate the promise of examining the genetic underpinnings of neural mechanisms in depression. While the three genetic polymorphisms noted here represent only a tiny fraction of the potential genes relevant to neuroimaging studies, additional studies are likely to further refine our understanding of gene-by-environment-by-brain interactions. To date, genetics and neuroimaging have not yet been combined in one single study of child or adolescent MDD. Such studies could tease apart models of brain development throughout the course of depression by examining brain function and structure in individuals with candidate gene positive or negative status prior to, during and after depressive episodes.

Discussion

Since the late 1990s, neuroimaging techniques have been applied with success to children and adolescents with current or historical depressive episodes or to those at increased risk for the development of MDD. The studies reviewed here support the hypothesis that, as in the adult MDD neuroimaging literature, pediatric MDD involves abnormalities spanning PFC, hippocampus, and amygdala networks. Volumetric studies initially highlighted significant anatomical network nodes, while fMRI with facial processing, cognitive control and reward processing tasks illuminated differences in activation in the same corticolimbic areas between depressed and control youth. In a move toward circuit-based approaches, a preliminary DTI study found lower FA in white matter tracts between the amygdala and subgenual ACC in depressed youth (Cullen, Klimes-Dougan et al. 2010). A similar functional circuit also involving the subgenual ACC was identified using functional connectivity methods acquired at rest (Cullen, Gee et al. 2009).

Moderating variables were especially evident in our review of the volumetric studies, the most widely published methodology in pediatric MDD. Differences attributed to gender and psychiatric comorbidity were evident in pediatric samples when examining pituitary, ACC and amygdala volumes. However, gender-related findings were not replicated across studies and sample sizes were small, so conclusions regarding gender effects in the pediatric neuroimaging literature are premature. Pubertal development was not systematically reported as a covariate of interest in the studies reviewed, although it should be systematically assessed in future studies as it likely has a measureable impact on brain structure and function.

Similar to samples in the adult depression literature, multiple authors noted that anxiety disorders were common in depressed subjects and may have affected findings in a number of studies. Externalizing comorbidities are less commonly mentioned in the childhood depression literature but were reported to contribute to neuroimaging findings reviewed here. Of note, ODD diagnoses impacted pituitary and PFC volumetric findings to a greater degree than any other diagnosis. Given longitudinal studies linking anxiety and externalizing disorders to adult forms of depression (Mason, Kosterman et al. 2004; Sourander, Jensen et al. 2007; Copeland, Shanahan et al. 2009), perhaps as or more robustly than even childhood depression, further neuroimaging work informing the link between MDD and these childhood disorders is needed.

Of interest, some findings have differed from those in the adult neuroimaging literature, possibly reflecting ongoing neuroplastic changes and the impact many years of depression have on neural connectivity. A number of authors also reported early neurobiological deficits that appear to predate medication use and cannot be attributed to stress-related damage from repeated episodes. While we lack longitudinal imaging data to fully support this assertion, we hypothesize, based on data from early onset depression and high-risk samples that some volumetric, functional and network-level brain differences *predate* psychopathology and have causal implications for the onset of depression, consistent with the “Early Abnormal” model (Figure 2). However, subsequent depressive episodes do appear to result in further neurotoxicity, based on changes evident in neuroimaging studies of depressed adults and adolescents. Such findings are consistent with all our proposed MDD models. However, without longitudinal data, the explanatory power of each model cannot be assessed with the present information and the lack of direct comparison between these models.

Despite enormous technological advances in neuroimaging over the past decade, our understanding of the neurobiological underpinnings of early-onset depression lags significantly behind that of adult depression, mirroring the relationship seen between child and adult psychiatry in many disorders. Tragically, early onset forms of MDD are associated with frequent recurrence and fewer opportunities for neural recovery, further highlighting the need for continued early intervention and research.

Recommendations for Future Work

Efforts should build on the recent findings in high-risk adolescents to better understand brain markers of disease susceptibility. Longitudinal studies are necessary to allow the field to chart out disease course by studying normal and abnormal changes that occur in adolescents with depression, spanning before their illness and after treatment. The addition of genetic information to these circuit-based neuroimaging findings in depressed youth would likely provide novel information on the contributions of genes to network functioning. Preliminary findings from the emerging functional connectivity and cortical thickness literatures suggest additional attention should also be paid to the investigation of regions outside of the typically described corticolimbic circuit as motor and parietal areas are also clearly implicated in depressive phenomenology. Continued work in child and adolescent neuroimaging holds the possibility of measuring connectivity-modulating interventions in developing brains, with the goal of preventing adverse adult outcomes.

References

Anand A, Li Y, et al. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. J Neuropsychiatry Clin Neurosci. 2007; 19(3):274–282. [PubMed: 17827412]

Anand A, Li Y, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry. 2005; 57(10):1079–1088. [PubMed: 15866546]

Anand A, Li Y, et al. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacology. 2005; 30(7):1334–1344. [PubMed: 15856081]

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000; 11(6 Pt 1):805–821. [PubMed: 10860804]

Baird AA, Gruber SA, et al. Functional magnetic resonance imaging of facial affect recognition in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1999; 38(2):195–199. [PubMed: 9951219]

Barnea-Goraly N, Menon V, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb Cortex. 2005; 15(12):1848–1854. [PubMed: 15758200]

Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B. 1996; 111(3):209–219. [PubMed: 8661285]

Bellani M, Baiano M, et al. Brain anatomy of major depression II. Focus on amygdala. Epidemiology and psychiatric science. 2011; 20(1):33–36.

Benes FM, Turtle M, et al. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch Gen Psychiatry. 1994; 51(6):477–484. [PubMed: 8192550]

Biswal B, Yetkin FZ, et al. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34(4):537–541. [PubMed: 8524021]

Boes AD, McCormick LM, et al. Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. Biol Psychiatry. 2008; 63(4):391–397. [PubMed: 17916329]

Bremner JD, Narayan M, et al. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000; 157(1):115–118. [PubMed: 10618023]

Burke JD, Hipwell AE, et al. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. J Am Acad Child Adolesc Psychiatry. 2010; 49(5): 484–492. [PubMed: 20431468]

Bussing R, Mason DM, et al. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. J Am Acad Child Adolesc Psychiatry. 2010; 49(6):595–605. [PubMed: 20494269]

Caetano SC, Fonseca M, et al. Medial temporal lobe abnormalities in pediatric unipolar depression. Neurosci Lett. 2007; 427(3):142–147. [PubMed: 17949901]

Caetano SC, Fonseca M, et al. Proton spectroscopy study of the left dorsolateral prefrontal cortex in pediatric depressed patients. Neurosci Lett. 2005; 384(3):321–326. [PubMed: 15936878]

Cascio CJ, Gerig G, et al. Diffusion tensor imaging: Application to the study of the developing brain. J Am Acad Child Adolesc Psychiatry. 2007; 46(2):213–223. [PubMed: 17242625]

Casey BJ, Jones RM, et al. The adolescent brain. Ann N Y Acad Sci. 2008; 1124:111–126. [PubMed: 18400927]

CDC. 2007

Cerasa A, Gioia MC, et al. Impact of catechol-O-methyltransferase Val(108/158) Met genotype on hippocampal and prefrontal gray matter volume. Neuroreport. 2008; 19(4):405–408. [PubMed: 18287936]

Chana G, Landau S, et al. Two-dimensional assessment of cytoarchitecture in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia: evidence for decreased neuronal somal size and increased neuronal density. Biol Psychiatry. 2003; 53(12):1086–1098. [PubMed: 12814860]

Chen HH, Rosenberg DR, et al. Orbitofrontal cortex volumes in medication naive children with major depressive disorder: a magnetic resonance imaging study. J Child Adolesc Psychopharmacol. 2008; 18(6):551–556. [PubMed: 19108659]

Chen MC, Hamilton JP, et al. Decreased hippocampal volume in healthy girls at risk of depression. Arch Gen Psychiatry. 2010; 67(3):270–276. [PubMed: 20194827]

Conturo TE, Lori NF, et al. Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci U S A. 1999; 96(18):10422–10427. [PubMed: 10468624]

Copeland WE, Shanahan L, et al. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. Archives of general psychiatry. 2009; 66(7):764–772. [PubMed: 19581568]

Cullen KR, Gee DG, et al. A preliminary study of functional connectivity in comorbid adolescent depression. Neurosci Lett. 2009; 460(3):227–231. [PubMed: 19446602]

Cullen KR, Klimes-Dougan B, et al. Altered white matter microstructure in adolescents with major depression: a preliminary study. J Am Acad Child Adolesc Psychiatry. 2010; 49(2):173–183. e171. [PubMed: 20215939]

Cunningham MG, Bhattacharyya S, et al. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol. 2002; 453(2):116–130. [PubMed: 12373778]

Dekker MC, Ferdinand RF, et al. Developmental trajectories of depressive symptoms from early childhood to late adolescence: gender differences and adult outcome. J Child Psychol Psychiatry. 2007; 48(7):657–666. [PubMed: 17593146]

Drevets WC, Price JL, et al. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008; 213(1–2):93–118. [PubMed: 18704495]

Drevets WC, Price JL, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997; 386(6627):824–827. [PubMed: 9126739]

Elliott R, Sahakian BJ, et al. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. Psychol Med. 1998; 28(3):559–571. [PubMed: 9626713]

Fair DA, Cohen AL, et al. The maturing architecture of the brain's default network. 2008:105.

Fair DA, Dosenbach NU, et al. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci U S A. 2007; 104(33):13507–13512. [PubMed: 17679691]

Fallucca E, MacMaster FP, et al. Distinguishing between major depressive disorder and obsessive-compulsive disorder in children by measuring regional cortical thickness. Archives of general psychiatry. 2011; 68(5):527–533. [PubMed: 21536980]

Farchione TR, Moore GJ, et al. Proton magnetic resonance spectroscopic imaging in pediatric major depression. Biol Psychiatry. 2002; 52(2):86–92. [PubMed: 12113999]

Fitzgerald PB, Oxley TJ, et al. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res. 2006; 148(1):33–45. [PubMed: 17029760]

Forbes EE, Christopher May J, et al. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. J Child Psychol Psychiatry. 2006; 47(10):1031–1040. [PubMed: 17073982]

Forbes EE, Hariri AR, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry. 2009; 166(1):64–73. [PubMed: 19047324]

Forbes EE, Shaw DS, et al. Alterations in reward-related decision making in boys with recent and future depression. Biol Psychiatry. 2007; 61(5):633–639. [PubMed: 16920074]

Fortier E, Noreau A, et al. Early impact of 5-HTTLPR polymorphism on the neural correlates of sadness. Neurosci Lett. 2010; 485(3):261–265. [PubMed: 20851164]

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8(9):700–711. [PubMed: 17704812]

Friston KJ, Frith CD, et al. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab. 1993; 13(1):5–14. [PubMed: 8417010]

Frodl T, Meisenzahl EM, et al. Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. Biol Psychiatry. 2003; 53(4):338–344. [PubMed: 12586453]

Fu CH, Williams SC, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry. 2004; 61(9):877–889. [PubMed: 15351766]

Fusar-Poli P, Placentino A, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci. 2009; 34(6):418–432. [PubMed: 19949718]

Gabbay V, Buchholz L, Gonen O. The neurochemistry of pediatric major depressive disorder. What do we know so far? Psychiatric Times. 2008:26–34.

Gabbay V, Hess DA, et al. Lateralized caudate metabolic abnormalities in adolescent major depressive disorder: a proton MR spectroscopy study. Am J Psychiatry. 2007; 164(12):1881–1889. [PubMed: 18056244]

Gaffrey MS, Luby JL, et al. Subgenual cingulate connectivity in children with a history of preschool-depression. Neuroreport. 2010; 21(18):1182–1188. [PubMed: 21048519]

Gallo V, Ghiani CA. Glutamate receptors in glia: new cells, new inputs and new functions. Trends Pharmacol Sci. 2000; 21(7):252–258. [PubMed: 10871893]

Giedd JN, Blumenthal J, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999; 2(10):861–863. [PubMed: 10491603]

Giedd JN, Snell JW, et al. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex. 1996; 6(4):551–560. [PubMed: 8670681]

Giedd JN, Vaituzis AC, et al. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. J Comp Neurol. 1996; 366(2):223–230. [PubMed: 8698883]

Goodman M, Hazlett EA, et al. Anterior cingulate volume reduction in adolescents with borderline personality disorder and co-morbid major depression. J Psychiatr Res. 2010

Gotlib IH, Hamilton JP, et al. Neural processing of reward and loss in girls at risk for major depression. Arch Gen Psychiatry. 2010; 67(4):380–387. [PubMed: 20368513]

Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol. 2008; 21(4):424–430. [PubMed: 18607202]

Greicius MD, Flores BH, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulated cortex and thalamus. Biol Psychiatry. 2007; 62(5):429–437. [PubMed: 17210143]

Halari R, Simic M, et al. Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naive adolescents with depression compared to controls. J Child Psychol Psychiatry. 2009; 50(3):307–316. [PubMed: 19175815]

Hamilton JP, Chen G, et al. Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Mol Psychiatry. 2010

Hamilton JP, Siemer M, et al. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry. 2008

Hariri AR, Drabant EM, et al. Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. Biol Psychiatry. 2006; 59(10):888–897. [PubMed: 16442081]

Huang H, Fan X, et al. White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. Neuropsychopharmacology. 2011; 36(3):684–691. [PubMed: 21085111]

Jacobs BL, van Praag H, et al. Adult brain neurogenesis and psychiatry: a novel theory of depression. Molecular psychiatry. 2000; 5(3):262–269. [PubMed: 10889528]

Kanner AM. Structural MRI changes of the brain in depression. Clinical EEG and neuroscience : official journal of the EEG and Clinical Neuroscience Society. 2004; 35(1):46–52.

Keedwell PA, Andrew C, et al. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005; 58(11):843–853. [PubMed: 16043128]

Kelly AM, Di Martino A, et al. Development of Anterior Cingulate Functional Connectivity from Late Childhood to Early Adulthood. Cereb Cortex. 2008

Kelly AM, Di Martino A, et al. Development of anterior cingulate functional connectivity from late childhood to early adulthood. Cereb Cortex. 2009; 19(3):640–657. [PubMed: 18653667]

Kempton MJ, Salvador Z, et al. Structural Neuroimaging Studies in Major Depressive Disorder: Meta-analysis and Comparison With Bipolar Disorder. Archives of general psychiatry. 2011; 68(7):675–690. [PubMed: 21727252]

Kim JE, Lyoo IK, et al. Laterobasal amygdalar enlargement in 6- to 7-year-old children with autism spectrum disorder. Archives of general psychiatry. 2010; 67(11):1187–1197. [PubMed: 21041620]

Kober H, Barrett LF, et al. Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. Neuroimage. 2008; 42(2):998–1031. [PubMed: 18579414]

Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009; 201(2):239–243. [PubMed: 19428640]

Kusumakar V, MacMaster FP, et al. Left medial temporal cytosolic choline in early onset depression. Can J Psychiatry. 2001; 46(10):959–964. [PubMed: 11816318]

Lau JY, Goldman D, et al. BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. Neuroimage. 2010; 53(3):952–961. [PubMed: 19931400]

Lawrence NS, Williams AM, et al. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry. 2004; 55(6):578–587. [PubMed: 15013826]

Liu Z, Xu C, et al. Decreased regional homogeneity in insula and cerebellum: a resting-state fMRI study in patients with major depression and subjects at high risk for major depression. Psychiatry Res. 2010; 182(3):211–215. [PubMed: 20493670]

MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. BMC Med. 2004; 2:2. [PubMed: 14969587]

MacMaster FP, Kusumakar V. MRI study of the pituitary gland in adolescent depression. J Psychiatr Res. 2004; 38(3):231–236. [PubMed: 15003427]

MacMaster FP, Mirza Y, et al. Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol Psychiatry. 2008; 63(4):385–390. [PubMed: 17640621]

MacMaster FP, Moore GJ, et al. Medial temporal N-acetyl-aspartate in pediatric major depression. Psychiatry Res. 2008; 164(1):86–89. [PubMed: 18703320]

MacMaster FP, Russell A, et al. Pituitary volume in treatment-naive pediatric major depressive disorder. Biol Psychiatry. 2006; 60(8):862–866. [PubMed: 16876142]

MacMillan S, Szeszko PR, et al. Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. J Child Adolesc Psychopharmacol. 2003; 13(1): 65–73. [PubMed: 12804127]

MacQueen GM, Campbell S, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A. 2003; 100(3):1387–1392. [PubMed: 12552118]

Mannie ZN, Norbury R, et al. Affective modulation of anterior cingulated cortex in young people at increased familial risk of depression. Br J Psychiatry. 2008; 192(5):356–361. [PubMed: 18450659]

Mason WA, Kosterman R, et al. Predicting depression, social phobia, and violence in early adulthood from childhood behavior problems. Journal of the American Academy of Child and Adolescent Psychiatry. 2004; 43(3):307–315. [PubMed: 15076264]

Matsuo K, Rosenberg DR, et al. Striatal volume abnormalities in treatment-naive patients diagnosed with pediatric major depressive disorder. J Child Adolesc Psychopharmacol. 2008; 18(2):121–131. [PubMed: 18439110]

Mayberg HS, Brannan SK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997; 8(4):1057–1061. [PubMed: 9141092]

Mazza JJ, Fleming CB, et al. Identifying trajectories of adolescents' depressive phenomena: an examination of early risk factors. J Youth Adolesc. 2010; 39(6):579–593. [PubMed: 20422348]

Mechelli A, Tognin S, et al. Genetic vulnerability to affective psychopathology in childhood: a combined voxel-based morphometry and functional magnetic resonance imaging study. Biol Psychiatry. 2009; 66(3):231–237. [PubMed: 19278671]

Mervaala E, Fohr J, et al. Quantitative MRI of the hippocampus and amygdale in severe depression. Psychol Med. 2000; 30(1):117–125. [PubMed: 10722182]

Mirza Y, Tang J, et al. Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. J Am Acad Child Adolesc Psychiatry. 2004; 43(3):341–348. [PubMed: 15076268]

Monk CS, Klein RG, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry. 2008; 165(1):90–98. [PubMed: 17986682]

Muetzel RL, Collins PF, et al. The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents. Neuroimage. 2008; 39(4):1918–1925. [PubMed: 18060810]

Nolan CL, Moore GJ, et al. Prefrontal cortical volume in childhood-onset major depression: preliminary findings. Arch Gen Psychiatry. 2002; 59(2):173–179. [PubMed: 11825139]

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Olvera RL, Caetano SC, et al. Reduced medial prefrontal N-acetyl-aspartate levels in pediatric major depressive disorder: a multi-voxel in vivo(1)H spectroscopy study. Psychiatry Res. 2010; 184(2): 71–76. [PubMed: 20864319]

Peterson BS, Warner V, et al. Cortical thinning in persons at increased familial risk for major depression. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(15):6273–6278. [PubMed: 19329490]

Pine DS, Cohen P, et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry. 1998; 55(1):56–64. [PubMed: 9435761]

Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2011; 36(1):183–206. [PubMed: 20861828]

Pizzagalli DA, Oakes TR, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Molecular psychiatry. 2004; 9(4):393–405. 325.

Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010; 35(1): 192–216. [PubMed: 19693001]

Rao U, Chen LA, et al. Hippocampal changes associated with early-life adversity and vulnerability to depression. Biol Psychiatry. 2010; 67(4):357–364. [PubMed: 20015483]

Roberson-Nay R, McClure EB, et al. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An FMRI study. Biol Psychiatry. 2006; 60(9):966–973. [PubMed: 16603133]

Rosenberg DR, Macmaster FP, et al. Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. Biol Psychiatry. 2005; 58(9):700–704. [PubMed: 16084860]

Rosenberg DR, Mirza Y, et al. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J Am Acad Child Adolesc Psychiatry. 2004; 43(9):1146–1153. [PubMed: 15322418]

Rosso IM, Cintron CM, et al. Amygdala and hippocampus volumes in pediatric major depression. Biol Psychiatry. 2005; 57(1):21–26. [PubMed: 15607296]

Sapolsky RM, Uno H, et al. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1990; 10(9):2897–2902. [PubMed: 2398367]

Savitz JB, Drevets WC. Imaging Phenotypes of Major Depressive Disorder: Genetic Correlates. Neuroscience. 2009

Schmidt-Wilcke T, Luerding R, et al. Striatal grey matter increase in patients suffering from fibromyalgia--a voxel-based morphometry study. Pain. 2007; 132 Suppl 1:S109–S116. [PubMed: 17587497]

Sexton CE, Mackay CE, et al. A Systematic Review of Diffusion Tensor Imaging Studies in Affective Disorders. Biol Psychiatry. 2009

Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biol Psychiatry. 2000; 48(8):791–800. [PubMed: 11063975]

Sheline YI, Barch DM, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 2001; 50(9): 651–658. [PubMed: 11704071]

Sheline YI, Gado MH, et al. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport. 1998; 9(9):2023–2028. [PubMed: 9674587]

Sheline YI, Price JL, et al. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A. 2010; 107(24):11020–11025. [PubMed: 20534464]

Smith EA, Russell A, et al. Increased medial thalamic choline found in pediatric patients with obsessive-compulsive disorder versus major depression or healthy control subjects: a magnetic resonance spectroscopy study. Biol Psychiatry. 2003; 54(12):1399–1405. [PubMed: 14675804]

Sourander A, Jensen P, et al. Who is at greatest risk of adverse long-term outcomes? The Finnish From a Boy to a Man study. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; 46(9):1148–1161. [PubMed: 17712238]

Spoletini I, Piras F, et al. Suicidal attempts and increased right amygdale volume in schizophrenia. Schizophrenia research. 2011; 125(1):30–40. [PubMed: 20869847]

Steffens DC, Byrum CE, et al. Hippocampal volume in geriatric depression. Biol Psychiatry. 2000; 48(4):301–309. [PubMed: 10960161]

Steingard RJ, Renshaw PF, et al. Smaller frontal lobe white matter volumes in depressed adolescents. Biol Psychiatry. 2002; 52(5):413–417. [PubMed: 12242057]

Steingard RJ, Renshaw PF, et al. Structural abnormalities in brain magnetic resonance images of depressed children. J Am Acad Child Adolesc Psychiatry. 1996; 35(3):307–311. [PubMed: 8714318]

Steingard RJ, Yurgelun-Todd DA, et al. Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. Biol Psychiatry. 2000; 48(11):1053–1061. [PubMed: 11094138]

Szeszko PR, MacMillan S, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology. 2004; 29(4):826–832. [PubMed: 14970831]

Takano K, Utsunomiya H, et al. Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. AJNR Am J Neuroradiol. 1999; 20(2):312–315. [PubMed: 10094362]

Thomas KM, Drevets WC, et al. Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry. 2001; 58(11):1057–1063. [PubMed: 11695953]

van Eijndhoven P, van Wingen G, et al. Amygdala volume marks the acute state in the early course of depression. Biol Psychiatry. 2009; 65(9):812–818. [PubMed: 19028381]

Veer IM, Beckmann CF, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Front Syst Neurosci. 2010; 4

Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta psychiatrica Scandinavica. 2000; 101(1):11–20. [PubMed: 10674946]

Whalen PJ, Bush G, et al. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry. 1998; 44(12):1219–1228. [PubMed: 9861465]

Whalen PJ, Shin LM, et al. Functional neuroimaging studies of the amygdala in depression. Semin Clin Neuropsychiatry. 2002; 7(4):234–242. [PubMed: 12382206]

Yao Z, Wang L, et al. Regional homogeneity in depression and its relationship with separate depressive symptom clusters: a resting-state fMRI study. J Affect Disord. 2009; 115(3):430–438. [PubMed: 19007997]

Yap MB, Whittle S, et al. Interaction of parenting experiences and brain structure in the prediction of depressive symptoms in adolescents. Arch Gen Psychiatry. 2008; 65(12):1377–1385. [PubMed: 19047524]

Yildiz-Yesiloglu A, Ankerst DP. Review of 1H magnetic resonance spectroscopy findings in major depressive disorder: a meta-analysis. Psychiatry Res. 2006; 147(1):1–25. [PubMed: 16806850]

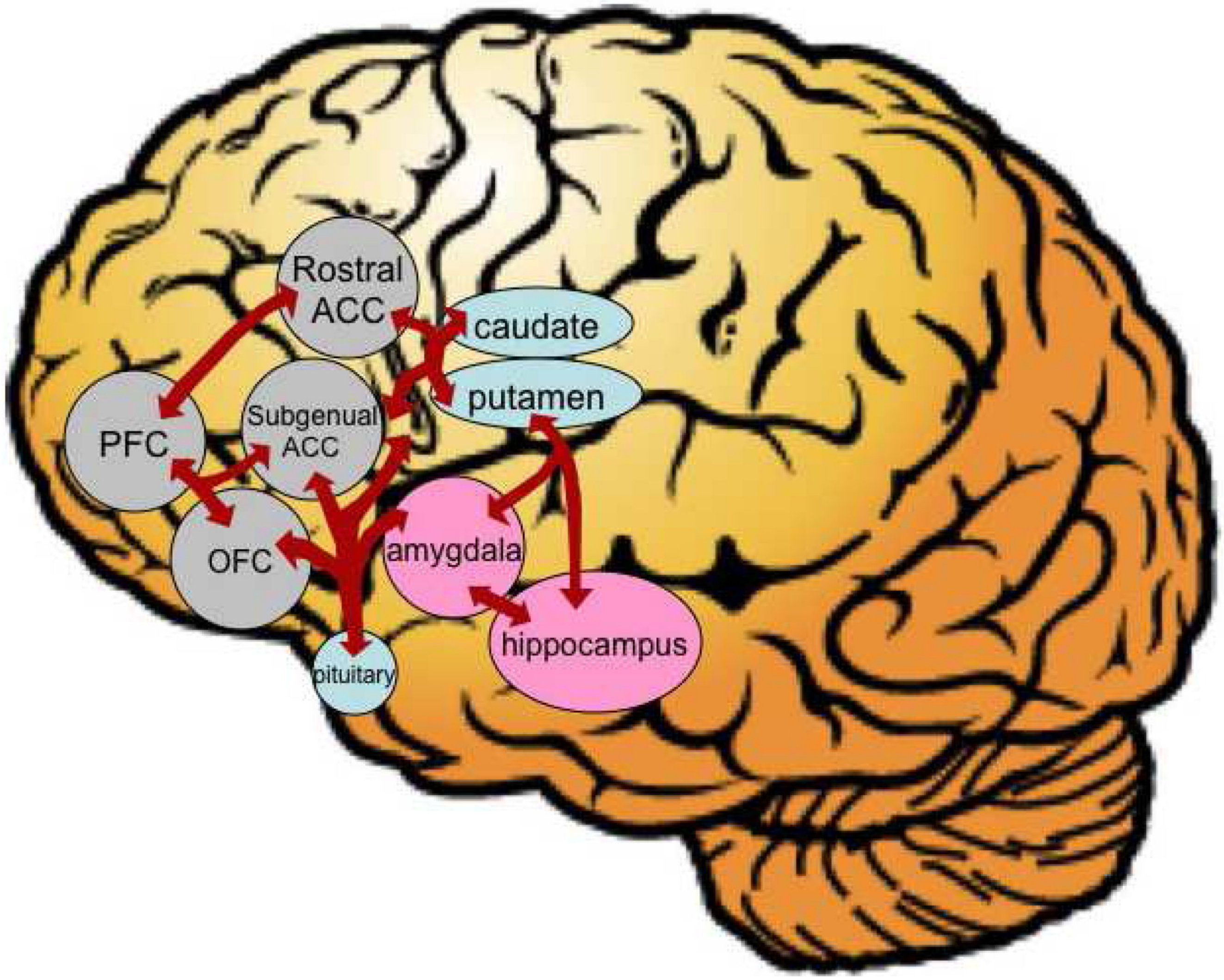

Figure 1.
Corticolimbic and striatal brain regions implicated in the pathophysiology of depression.

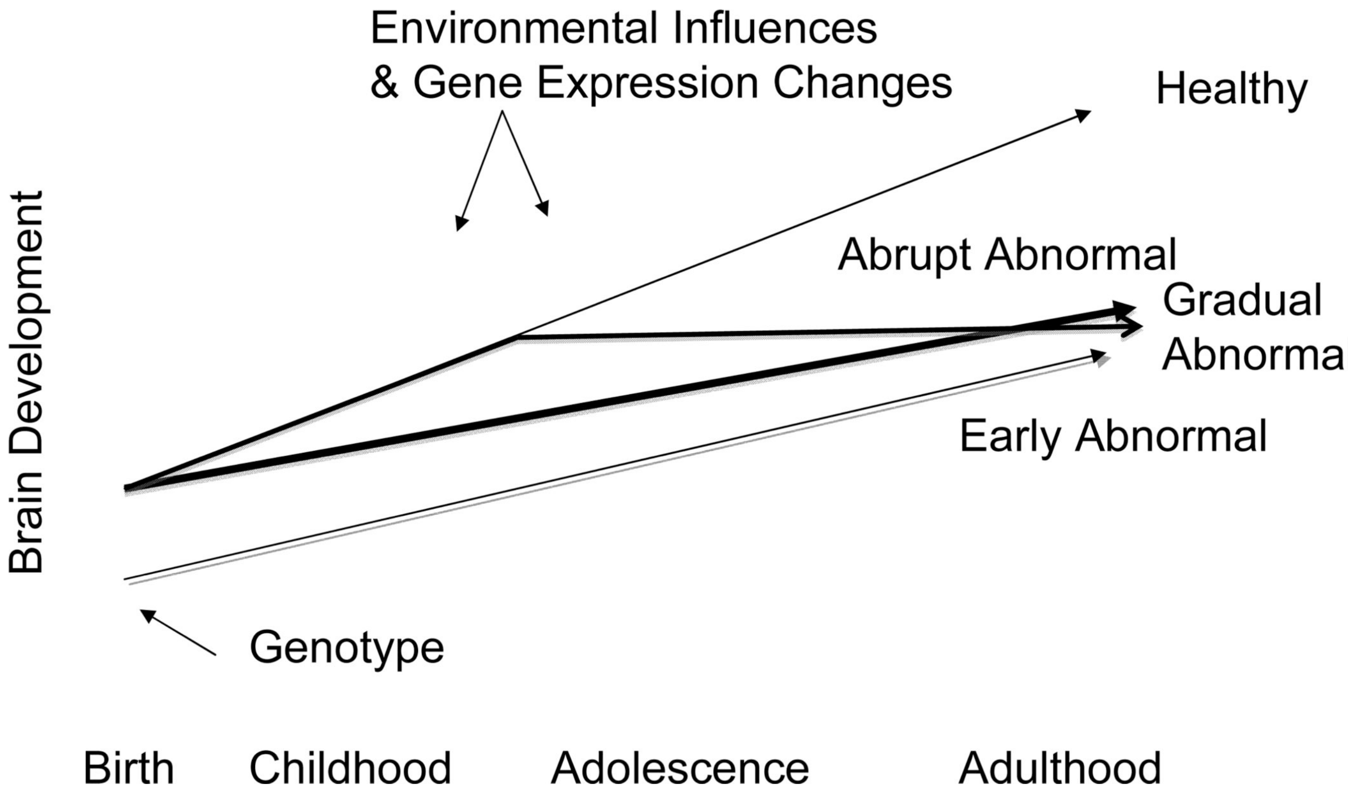

Figure 2.
Mechanisms of altered trajectories for healthy brain circuitry in the development of MDD

Table 1

Volumetric MRI studies of child and adolescent depression.

Study	Sample	Age (years)	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbid-ity	Significant findings in MDD compared to controls	Imaging methods
Steingard et al., 1996	65 DD (56 MDD + 9 dysthymia) 18 PC (all subjects were psychiatrically hospitalized)	13.42±2.32 10.78±2.92	30M 13M	NR	NR	NR	NR (likely medicated)	PC: CD/ODD (n=11); ADHD (n=2); PTSD (n=3); Adjustment Disorder (n=2) Dx based on chart reviews	Smaller frontal lobe/ cerebral volume ratio and lateral ventricular/cerebral volume ratio	1.5 T 5mm Digitized from film
Steingard et al., 2002	19=MDD 38=HC	15.4 ±1.9 14.6 ±1.5	2M (11%) 13M (34%)	NR	25.9± 21.7 months	NR	No current Psychotropic medication use (> 3 months); n=3 had prior trials	NR (routine exclusions)	Smaller **whole brain** volumes & **frontal white matter** volumes. Larger **frontal gray matter** volumes	1.5 T 1mm gap 1.5mm
MacMillan et al., 2003	23 MDD 23 HC	8–17	10M 10M	11.84± 3.07	NR	NR	Psychotropic naive	NR (routine exclusions)	Larger L and R **amygdala/hippocampus** volume ratio, associated with anxiety, not MDD severity	1.5T Traced Anatomic boundaries
MacMaster and Kusumakar, 2004a	17 MDD 17 NC	16.67±1.83 16.23±1.61	8M 8M	14.06 ± 1.98	2.89 ± 1.71 years	9 MDD subjects had FH of mood disorder	All but 3 subjects were psychotropic naive	Substance abuse (n=2); ODD (n=1); No anxiety disorders	L **hippocampal** volumes were reduced in MDD. **Hippocampal** size was negatively correlated with the age of onset of depression	1.5 T 1.5 mm 1.5mm gap
Rosso, et al., 2005	20 MDD 24 HC	15.35±.34 14.08±.31	3M (85% F) 4M	12.8 ±1.8 years	2 years (2–72 months)	16 with first degree relative with MDD	Off meds for >3 months. 5/20 treated in past with antidepress-ants	ODD (*n*= 3); Panic Disorder (*n*=2).	Smaller **amygdala** volumes, but no **hippocampal** volume differences. Age at onset was significantly associated with R **hippocampal** volumes	1.5T 1.5mm 1 mm gap ROI
Caetano et al, 2007	19 MM 24 HC	13.0±2.4 13.9±2.9	13M 13M	10.3±2.3	27.4±12.2 months	17 with mood disorders in first degree relatives	N=9 on antidepressant N=6 stimulants	ADHD (n=7); GAD (n=7); social phobia (n=2); panic disorder (n=1); ODD (n=1)	Smaller L **hippocampal** volumes, but no differences in **amygdala** volumes	1.5 T 1.0 mm 0 gap ROI

Study	Sample	Age (years)	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbid-ity	Significant findings in MDD compared to controls	Imaging methods
MacMaster et al., 2008	32 MDD 35 HC	14.08±2.88 14.51±2.72	12 M 13M	NR	27.7 months	MDD: At least one first degree relative with MDD; None with BP Disorder. HC: No family DSM-IV disorders.	Psychotropic naive	56% with "significant anxiety"	Smaller **hippocampal** volumes were found in depressed pediatric patients with familial MDD compared to healthy controls; no group volumetric differences were observed for the **amygdala**	1.5 T 1.5mm
Nolan et al., 2002	22 MDD 22 HC	9–17 9–17	10M 10M	12.18±2.68 years	NR	12 patients had at least 1 first-degree relative with MDD. None with bipolar disorder.ODD predominate non-familial group;	Psychotroic naive	anxiety disorders (n=7); ODD (n=4); ADHD (n=2), dysthymia (n=1)	Larger L **Prefrontal Cortex** volume in non-familial MDD	1.5T 1.5 mm
Boes et al, 2008	112 HC	12.08±(2.5)	59 M	NA	NA	32 subjects with nuclear family member with MDD	NR	No learning or psychiatric disorders	Depressive symptoms correlate with significantly lower rostral **Anterior Cingulate** volumes; stronger correlation with +FH of MDD	1.5T 1.5 mm
MacMaster and Kusumakar, 2004b	17 MDD 17 NC	16.67±1.83 16.23±1.61	8M 8M	14.06±1.98 years	2.89±1.71 years	9 MDD subjects had FH of mood disorders	3 subjects recently started medications; others psychotropic naive	Substance abuse (n=1); ODD (n=1)	Increased **pituitary** volume in MDD	1.5T 1.45mm
MacMaster et al, 2006	35 MDD 35 NC	14.49±2.53 14.33±2.46	15M 15M	11.85±3.21 years	22.79±24.38 months	19 with MDD in first degree relatives	Psychotropic naive	Multiple ODD cases(associate ion with pituitary volumes) cases; Routine exclusions	Larger **pituitary** volume in MDD males	**1.5T** **1.5mm**
Matsuo et al, 2009	27 MDD 26 HC	14.4 ±2.2 14.4 ±2.3	10M 12M	141.0±36.3 months	38.8±34.3 months	11 with first degree relatives with psychiatric disorders	Psychotropic naive	n=4 with ADHD; n=9 no Comorbidities ; n=9 Anxiety disorders;	Smaller R **striatal** and R **caudate** volumes	**1.5 T** **1.5 mm**

Study	Sample	Age (years)	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbid-ity	Significant findings in MDD compared to controls	Imaging methods
								n=6 CD; n=1 eating disorders		
Peterson et al, 2009	66 HR 65 LR	6–54 years	NR	NR	NR	HR have parent or grandparent with MDD	NR	Groups similar in severity of anxiety and depression	Large expanses of cortical thinning across the lateral surface of the right cerebral hemisphere in persons at high risk	**3T Cortical Thickness**
Yap et al., 2008	106 HC	12.5±0.5	55M	NA	NA	NR	NR	No mood,, Substance use, or eating disorder. High and Low tempera-mental risk for mental health prob-lems were oversampled; 10 had Axis I disorders	Boys with smaller R **amygdala** volumes reported more depressive symptoms; **hippocampal** and **anterior cingulate** volumes not related to the level of depressive symptoms. Maternal aggression moderated the associations between both the **amygdale** and **anterior cingulated** volumes and adolescent depressive symptoms	**3T 1.5mm contiguous**
Rao, Chen, et al., 2010	29 MDD 22 FH 32 HC	12–20	42M 41F	NR	NR	None with BP Disorder. At least 1 biological parent with MDD.	Psychotropic agent free for at least 8 weeks.	n=2 anxiety; n=2 motion artifacts.	Smaller **hippocampal** volume bilaterally	**1.5 T 1.2 mm**
Goodman, Hazlett, et al., 2010	13 BPD/MDD 13 HC	15.8 16.2	6M 20F	NR	NR	NR	NR	39% ADHD, 39% ODD, 15% Substance abuse, 8% PTSD	Reduced **BA24** gray matter volume	**3 T .82 mm**
Falluca et al, 2011	24 MDD 24 OCD 30 HC	13.96 13.02 14.11	9M 8M 10M	NR	24.9 mo 41.17 mo	Most MDD had first degree relative with MDD	Antidepressant naive	MDD group: 15/24 ADHD, ODD or Anx. Disorders	Thinned pericalcarine, postcentral, superior parietal gyrus in MDD. Thicker temporal pole.	**3T Cortical Thickness**

Abbreviations: HC=healthy controls; MDD=subjects with Major Depressive Disorder; PC=psychiatric controls NA=not applicable; NR=not reported; Dx=diagnosis; FH=family history; HR=high risk; LR=low risk; R=right; L=left; ODD= Oppositional Defiant Disorder; CD=conduct disorder. Routine exclusions: mental retardation, autism/pervasive developmental disorders, psychosis, bipolar disorder.

Table 2

Task-based functional neuroimaging studies of child and adolescent depression.

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC	Task
Thomas et al., 2001	5 MDD 12 HC 12 Anxiety (11 GAD + 1 Panic Disorder)	12.3±2.7 12.2±2.6 12.8±2.1	0M 7 M 7M	NR	NR	NR	No medication for 2 weeks prior to scan	One subject with GAD had comorbid social phobia. Two had comorbid GAD.	Anxious children showed exaggerated response to fearful faces while MDD showed *blunted* response in L **amygdala**	Task: "Rapid (1 Hz) and successive presentation of a standard photographic set of faces in blocks of neutral and fearful expressions."
Roberson-Nay et al, 2006	10 MDD 23 HC 11 anxious (separation anxiety disorder (*n* =3), social phobia (*n*=3), and GAD (*n*=9))	13.8±(2.7) 14.8±(2.2) 11.5±(1.5)	3M 10M 7M	NR	NR	NR	"medication free"	4 of MDD group had a comorbid anxiety disorder	*Heightened* L **amygdale** activation during encoding of images of emotional expressions	**Facial Encoding:** Viewed adult actors depicting one of four face-emotions. Followed by recognition task after scanning
Halari et al, 2009	21 MDD 21 HC	16.2±(.83) 16.3±(1.1)	10M 10M	"first episode MDD"	NR	NR	"medication naïve"	"Comorbidity with other major psychiatric disorders was excluded"	In all tasks of executive function, MDD group had *reduced* activation in **R DLPFC, inferior prefrontal cortex (IFC)** and **anterior cingulate gyrus (ACG)**	Selective attention (Simon task), attentional switching (Switch task), motor response inhibition and error detection (Stop task)
Forbes et al, 2006	14 MDD 17 HC	14.73 ±(1.49) 14.45 ± (1.79)	3M 7M	NR ("currently depressed")	NR	NR	"free of psychotropic medications, cigarettes, and illicit drugs"	MDD: dysthymia (2), generalized anxiety disorder (10), social phobia (5), panic disorder (1), and separation anxiety	Decision phase: MDD showed *blunted* responses in the **ACC**, **caudate nuclei**, and **OFC**. Outcome phase: MDD had *diminished*	Reward decision making and outcome: choose between constant or varying magnitude and probability of

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC	Task
								disorder (1).	responses in the **ACC**, **caudate**, and **OFC**, but **amygdale** *hyperactivation*	reward
Forbes et al, 2009	15 MDD 28 HC	13.5 ± (2.1) 13.1 ± (2.6)	5M 7M	NR	NR	Some parents with MDD	"free of psychotropic medications, cigarettes, and illicit drugs"	MDD: GAD (8), social anxiety (3), panic disorder (1)	MDD had *less* **striatal** response during reward anticipation and reward outcome, but *more response* in **dorsolateral** and **medial prefrontal cortex**	Guess value of card for monetary reward with anticipation and outcome period for each trial
Monk, Klein, et al, 2008	17 FH 22 HC	10–18	19M 20F	NR	NR	Parents had been patients at mood and anxiety disorder clinics for MDD	Free of psychoactive drugs	n=13 past anxiety disorder, n=2 past ADHD, n=1 ODD	*Greater* **amygdala** and **nucleus accumbens** activation to fearful faces, *less* **nucleus accumbens** to happy faces	Patients passively viewed, subjectively rated, and determined nose width in a set of faces varying in intensity of happy or fearful expressions, including neutral
Mannie, Norbury, et al, 2008	18 FH 16 HC	19–21 18–21	15M 19F	NR	NR	At least biological parent with MDD	NR	NR	Altered modulation of **anterior cingulated cortex**	Modified Stroop "name the number of words task", Shown words that are neutral, physically or socially threatening, or positive; Asked to give the number of words displayed at the end of each trial.

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC	Task
Gotlib, Hamilton, et al, 2010	13 FH 13 HC	10–14	26F	NR	NR	Mothers with at least 2 episodes of past MDD	NR	FH-Mothers of subjects: past OCD(1), past PTSD & panic disorder(1), past bulimia & specific phobia(1)	FH show anomalies in **striatum**, **insula** and **dACC** activations	Modified KIDMID, earn points to redeem prizes instead of money.

Table 3

Chemicals measured in proton MRS brain imaging, their commonly held biological functions and findings suggested by abnormal MRS peak findings.

Chemical Peak	Biological function	Pathology implicated in abnormal peak
N-Acetyl-Aspartate (NAA)	Marker of neuronal density, energy homeostasis & myelin production	Neuronal loss/dysfnction
Creatine (Cr)	Used as an internal standard of energy utilization for comparison	--------
Choline (Cho)	Membrane density, phospholipid metabolism	Cell membrane breakdown (i.e., neuronal injury, malignancy)
Myoinositol (mI)	Marker of glial proliferation	Brain Inflammation
Lactate (Lac)	Failure of aerobic Oxidation	Ischemia, seizures, metabolic disorders
Glutamate (Glu)	Major excitatory neurotransmitter	Difference in regional Glu levels
GLX	A peak containing Glu, GABA and glutamine neurotransmitters	Difference in regional GLX levels

Table 4

Magnetic resonance spectroscopy studies of child and adolescent depression.

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC
Rosenberg et al, 2000 (abstract)	13 MDD 13 HC	9–17 Case-matched	NR	NR	NR	NR	Psychotropic naive	NR	greater concentrations of L caudate glutamate/glutamine/GABA and choline compounds
Steingard et al, 2000	17MDD 28 HC	15.8 ± (1.6) 14.5 ± (1.7)	3M 10M	NR	NR	18% of control group had +FH mood disorders; 47% for MDD group	Psychotropically treated (n=4)	Routine exclusions; MDD: Anxiety disorders (n=3)	higher orbitofrontal cortex choline/creatine and choline/N-acetylaspartate ratios
Kusumakar et al., 2001	11 MDD 11 HC	16.73 ± (1.7) 16.66±(1.4)	6M 6M	NR	NR	NR	NR	Routine exclusions	Lower left amygdalar choline/Cr ratios
Farchione et al., 2002	11 MDD 11 HC	14.33±(1.93) 14.43±(2.04)	4M 4M	12.14±(2.99)	1.84±(1.96)	None in HC; NR for MDD	Treatment naive	Anxiety Disorders (4); ODD (1); dysthymia (2); ADHD (1)	higher choline concentration left dorsolateral prefrontal cortex
Smith et al, 2003	18 MDD 18 HC 27 OCD	14.38±2.50 14.40±2.68 10.31±2.48	9M 9M 13M	NR	1.66 ± 1.55 2.63 ± 2.60	None in HC; NR for MDD	Psychotropic Naive	MDD: Anxiety (5); ODD (5); ADHD (4); dysthymia (1)	thalamic choline concentrations did not differ between groups
Mirza et al, 2004	13 MDD 13 HC	15.54 ± 2.39 15.36 ± 2.48	5M 5M	12.17 ± 1.12	3.16 ± 3.65	None in HC; NR for MDD	Psychotropic Naive	Anxiety (6), ADHD(1), ODD (3)	Glutamatergic concentrations were lower in anterior cingulate cortex
Rosenberg et al, 2004	14 MDD 14 HC 20 OCD	15.63 ± 2.33 15.47 ± 2.42 11.39 ± 2.83	5M 5M 9M	NR	3.15 ± 3.51 3.87 ± 3.46	None in HC; NR for MDD	Psychotropic Naive	anxiety disorders (7); ODD (2); ADHD (1)	Glutamatergic concentrations were lower in the anterior cingulate cortex
Caetano et al, 2005	13 MD 22 HC	13.3±2.3 13.6±2.8	10M 13M	NR	NR	None in HC; NR for MDD	6 on medications; 6 psychotropic naive	Anxiety and ADHD	lower levels of choline containing compounds and higher levels of myoinositol levels in dorsolateral PFC
Rosenberg et al, 2005	14 MDD 14 HC	15.63±2.33 15.47±2.42	5 M 5M	NR	NR	Same subjects as Mirza et al, 2004 and Rosenberg et al, 2004	Psychotropic naive	L handedness (see above)	Reduced anterior cingulate glutamate, not glutamine levels
Gabbay et al, 2007	14 MDD 10 HC	16.2±2.1 16.1±1.9	6M 4M	NR	17.36 months	7 had FH of MDD	50% MDD on psychotropics	MDD: social phobia (n=2), ADHD(n=1)	elevated concentrations of choline and creatine in L caudate

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Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC
MacMaster et al, 2008	11 MDD 11 HC	14.13±1.99 14.48±1.82	6M 6M	NR	NR	NR	Treatment naive	Routine exclusions	lower N-acetyl-aspartate in L medial temporal cortex
Olvera, et al 2010	16 MDD 38 HC	8–17	30M 24F	10.31 years	28.5 months	n=15 first degree relative with mood disorder	n=7 medicated	NR	R AC decreased NAA and GPC+PC with trend for decreased PCr+Cr, lower NAA in R MPFC and trend for decreased GPC+PC

Table 5

Other neuroimaging studies of child and adolescent depression.

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC
Cullen et al, 2009	12 MDD 14 HC	15–19	9M 17F	NR	2+ years	NR	n=10 treated with medication, n=1 medication naïve, n=1 medication free 1 month prior to scan	n=7 GAD, n=3 social phobia, n=2 PTSD, n=3 ADHD, n=4 past substance use disorder but free of use for 2 months	Decreased functional connectivity within key neural circuit arising from subgenual ACC
Mechelli et al, 2009	14 Met/Met 22 Met/Val 14 Val/Val	10–12	50M OF	NR	NR	NR	NR	NR	met158 allele was also positively associated with gray matter volume in the left hippocampal head
Gaffrey, et al	17 PO-MDD 15 HC	9.6±.93 9.5±1	13M 19F	Before age 6	Not required to meet 2 week criterion	NR	Medication naive	NR	Increased connectivity between R sgACC and inferior frontal gyrus (BA 47) and thalamus, increased connectivity between L sgACC and periaqueductal gray, precuneus (BA7), and paracentral lobule (BA5)
Cullen, et al, 2010	14 MDD 14 HC	15–19	10M 18F	NR	2+ years	NR	n=11 treated with medication, n=1 medication naïve, n=2 medication free 1 month prior to scan	n=7 GAD, n=3 social phobia, n=1 panic disorder, n=2 PTSD, ¼ ADHD, 1/3 past substance use disorder but free of use for 2 months	Lower FA in specific WM tracts, lower FA in tract connecting sugenual ACC to amygdale in R hemisphere
Huang, et al	18 FH 13 HC	12–20	14M 17F	NR	NR	At least one biological parent with MDD	NR	NR	Lower FA levels in white matter tracts including L cingulum bundle, L & R superior longitudinal fasciculus, L & R combined bundles of uncinate, and inferior fronto-occipital fasciculus, and the splenium
Fortier, et al, 2010	24 L group 24 S group	4mo-8yrs	23M 25F	NR	NF	NR	NR	NR	During a sad state induced by film excerpts, children carrying either one or two copies of the S allele, compared to children

Study	Sample	Age	Gender	Age of onset	Duration of illness	Family history	Medication status	Comorbidity	Findings compared to HC
									homozygous for the L allele, show increased activations in brain regions (putamen, caudate nucleus, rostro-ventral ACC) known to be associated with normal sadness and major depression.
Lau, et al, 2010	27 anxiety and/or MDD 31 HC	9–18 9–17	26M 32F	NR	NR	NR	Non-medicated	n=21 anxiety disorder, n=12 GAD, n=12 social phobia, n=5 separation anxiety disorder, n=4 GAD only, n=4 social phobia only, n=1 separation anxiety only, n=13 MDD, n=5 MDD only	Met-carriers showed greater neural responses than Val-homozygotes. Such genotype differences were absent in healthy adolescents, M*et* allele enhanced amygdala and hippocampal activation, comparable predictions of neural activity did not characterize healthy adolescents