IMAGING AND NEUROCIRCUITRY OF PEDIATRIC MAJOR DEPRESSION

David R. Rosenberg, Frank P. MacMaster, Yousha Mirza, Phillip C. Easter

Summary

Object: Major depressive disorder (MDD) is a chronic and debilitating condition. MDD commonly emerges in childhood and adolescence and is continuous with adult forms of the illness.

Method: The authors review existing brain imaging literature on the neurobiology of pediatric depression.

Results: Past structural imaging studies noted abnormalities in the frontal lobe, amygdala, hippocampus and pituitary gland in pediatric MDD. Previous studies of neurochemistry found alterations in glutamatergic, choline and creatine concentrations in pediatric MDD.

Conclusions: The authors argue for increased efforts towards identifying relevant biomarkers in MDD that may aid in diagnosis of and development of new treatments for the illness.

Key Words: Major Depressive Disorder – Neurobiology - Pediatric Depression

Declaration of interest: None

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Introduction

Our understanding of the neurobiologic underpinnings of pediatric major depressive disorder (MDD) has lagged far behind treatment development. However, there is substantial progress in understanding the brain mechanisms involved in the pathogenesis and treatment response of MDD. Here we detail this exciting story to set the stage for the next generation of experiments. This article describes a multidisciplinary approach incorporating and translating advances in developmental neuroscience into enhanced neurodiagnostic assessment and treatment development.

Clinical Characterization and Assessment

MDD is a severe and typically chronically disabling neuropsychiatric disorder with considerable morbidity, family burden and mortality risk (Essau and Dobson 1999, Angold et al. 1998, Lewinsohn et al. 1993a, b). The point prevalence for pediatric MDD is 1 in 20 adolescents (Essau and Dobson 1999, Lewinsohn et al. 1993a). The lifetime prevalence of pediatric MDD is 15%-20%, which is comparable to prevalence rates of adult MDD (Lewinsohn et al. 1993b, Kessler et al. 1994, Lewinsohn et al. 1986). Approximately 6% of adolescents currently meet criteria for MDD and about 25% have met criteria for MDD by late adolescence (Kessler et al. 2001). Depression is a common contributor to suicide in adolescents, now the third leading cause of death in teenagers (Brent et al. 1996, Arias et al. 2003). MDD in youth is continuous with adult MDD and a risk factor for MDD, suicide and long-term psychosocial impairment in adulthood (Essau and Dobson 1999, Pine et al. 1999, Weissman et al. 1999). This underscores that MDD in youth is a highly prevalent condition with significant public health importance.

Developmental neurobiology

Neurobiological studies using various techniques in several laboratories have provided converging lines of evidence supporting prefrontal cortical-striatal and medial temporolimbic dysfunction as a basis for MDD (See Soares and Mann 1997a for review) (Figure 1). Indeed, one of the more striking findings over the past decade in adult and pediatric neuropsychiatric research in depression is the common theme of correlation of alterations in anterior cingulate volume, perfusion and metabolism with a change in depressive symptoms (Mirza et al. 2004, Bench et al. 1995, Botteron et al. 2002, Drevets et al. 1992, Drevets et al. 1997, Ebert

Received November 2005, accepted May 2006

and Ebmeier 1996, Goodwin 1996, Drevets et al. 1998, Goldapple et al. 2004, Kaufman et al. 2003). Changes are usually not limited to the cingulate but include basal ganglia and other paralimbic structures. There are unique directional changes in this circuitry in adult patients with MDD with pharmacotherapy vs. psychosocial interventions (Goldapple et al. 2004, Kennedy et al. 2001, Brody et al. 2001, Martin et al. 2001, Mayberg 2002). The last several years have seen a series of longitudinal studies in adult patients with MDD that are increasing our understanding of the functional neuroanatomy and neurochemistry of MDD. Cingulate-paralimbic-basal ganglia computational functions are a property of the circuit as a whole. Thus, the behavioral/symptomatic consequences of dysregulation in this circuitry in depression may depend upon lesion specific neurochemical factors that at least in theory, may be differentially modifiable by psychosocial or pharmacological treatment approaches working via the same or different mechanisms. More recent investigation in youth with MDD has begun to test new clinical neurodevelopmental models, and by inference is embracing the science-based trend toward conceptualizing mental illness within a medical framework (Hyman 2000).

Volumetric Alterations in Pediatric MDD

Frontal Lobe

Steingard et al. (2002) reported smaller frontal lobe white matter volumes and larger frontal lobe gray matter volumes in adolescents with MDD vs. healthy adolescents even after controlling for age and whole brain volume. Pioneering work by Drevets and colleagues (see Drevets 2000 for review) noted striking localized left but not right hemispheric reduction in the subgenual region of the prefrontal cortex (SGPFC) associated with decreased cerebral blood flow that was most pronounced in familial patients with MDD (at least one first degree relative with mood disorder). Nonfamilial patients with MDD (no obvious family history of mood disorder) do not differ from healthy volunteers in left or right SGPFC volume. Botteron et al.(2002) also found significant volumetric reductions (19%) in left but not right SGPFC in 30 women 18-23 years of age with early onset MDD and 18 women 24-52 years of age that were comparable in both age groups as compared to controls.

Nolan et al.(2002) studied 22 psychotropic-naïve pediatric patients with MDD 9-17 years of age vs. 22 age and sex-matched healthy comparison subjects. They found that pediatric patients with nonfamilial MDD had significantly increased left but not right prefrontal cortical volumes compared to both patients with familial MDD (17% bigger) and healthy controls (11% larger) (Figure 2). These left prefrontal volumetric abnormalities remained significant even after controlling for severity of anxiety, which suggested that left prefrontal cortex may be an integral site in the pathogenesis of pediatric MDD. Left prefrontal cortical volume correlated with severity of depression in familial but not in nonfamilial pediatric patients with MDD (Nolan et al. 2002). Smaller left prefrontal cortical volumes in familial patients with MDD demonstrated a correlational trend with increased duration of illness. Taken together, decreased left prefrontal cortical volume in familial patients with MDD in youth and adults (Drevets et al. 1992, Drevets et al. 1997, Nolan et al. 2002) could result from degeneration of left prefrontal cortical volume. Whereas larger left prefrontal cortical volumes in pediatric patients with nonfamilial MDD could result from developmental alterations in prefrontal cortical maturation.

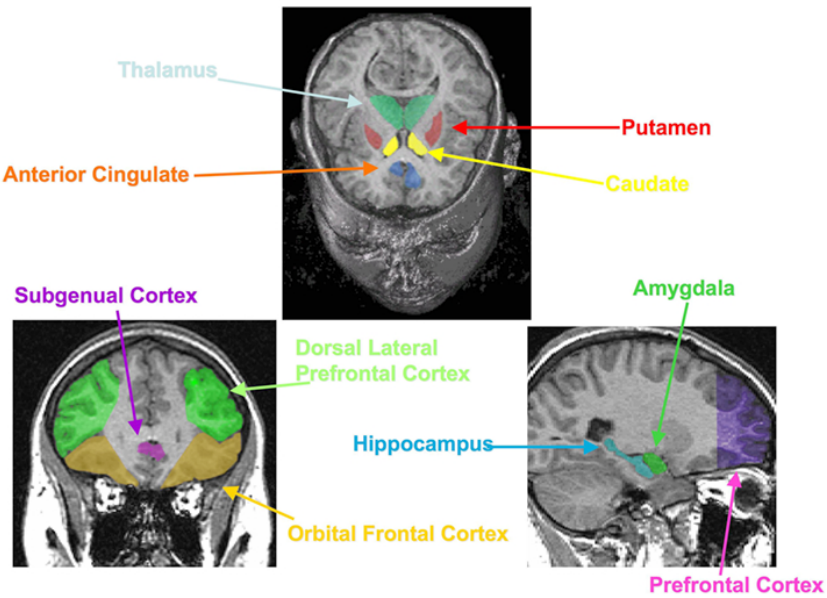


Figure 1. *Circuits implicated in pediatric major depressive disorder*

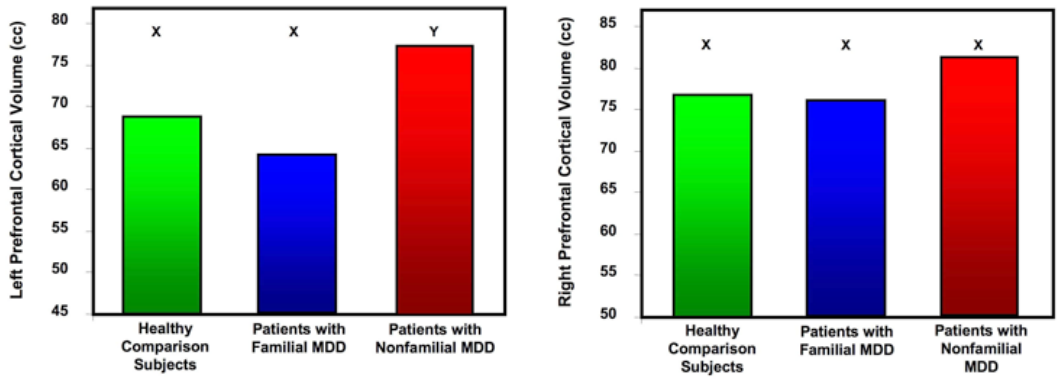


Figure 2. *Left and right prefrontal cortical volume in healthy comparison subjects, patients with familial MDD and patients with non-familial MDD. Groups showing a differing letter are significantly different. MDD = major depressive disorder*

Amygdala and Hippocampus

The amygdala and hippocampus play a key role in regulating emotion in health and disease (Aggleton 1992, Davidson and Irwin 1999, Davis 1994, Halgren et al. 1978, Lane et al. 1997, LeDoux 1996, Papez 1937, Phelps and Anderson 1997). Frodl et al.(2002a) reported increased right and left amygdala volumes in 30 first episode young adults with MDD vs. 30 age and sex-matched healthy comparison subjects. In contrast, Frodl et al.(2003) found no amygdala enlargement in patients with recurrent MDD. Tebartz van Elst et al.(2000) has also found that adult patients with MDD and temporal lobe epilepsy had significantly increased amygdala volumes vs. both healthy comparison subjects and patients with temporal lobe epilepsy who did not have comorbid MDD. Adult patients with a first episode of MDD vs. healthy comparison subjects have demonstrated decreased hippocampal volumes (Frodl et al. 2002b), as have patients with more chronic illness (Bremner et al. 2000, Sheline et al. 1996, Sheline et al. 1999, Steffens et al. 2000).

Medial temporal lobe regions such as the amygdala and hippocampus undergo striking maturational changes during childhood and adolescence (Giedd et al. 1996, Pfluger et al. 1999, Yurgelun-Todd et al. 2003). Consistent with prior investigation in adults with MDD (Sheline et al. 1999), MacMaster & Kusumakar (2004a) reported decreased hippocampal volumes in MDD patients vs. controls. Duration of depression correlated with hippocampal volume in this sample. This investigation did not report on amygdala volume. MacMillan et al.(2003) reported significantly larger amygdala: hippocampal volume ratios in 23 treatment-naïve pediatric patients with MDD 8-17 years of age vs. 23 age and sex-matched healthy comparison subjects (Figure 3). These alterations in pediatric patients with a primary diagnosis of MDD were more associated with severity of anxiety than with severity of depression (Figure 4).

Findings of increased amygdala hippocampal volumes associated with increased severity of anxiety but not depression may suggest a differential impact of comorbidity on brain anatomy. Given that comorbid anxiety disorders are especially relevant in pediatric MDD (Birmaher et al. 1996a, b), this may be especially relevant. Pine et al.(2001) also found that high levels of fear in adolescence predicted later episodes of MDD. Sheline et al.(2001), using functional magnetic resonance imaging (fMRI), demonstrated increased amygdala activation in adult MDD patients when shown masked emotional faces. The amygdala activation in patients was highest when shown fearful faces. After treatment with the selective serotonin reuptake inhibitor, sertraline, formerly increased amygdala activation decreased to levels not significantly different from healthy volunteers. Thomas et al. (2001), using fMRI, found altered amygdala function in both depressed and anxious children (8 -16 years of age) that were shown fearful faces. This signal change in the amygdala was most associated with the severity of the child's anxiety. DeBellis et al.(2000) conducted a volumetric MRI study and found increased amygdalar volumes in 12 pediatric patients with generalized anxiety disorder vs. 24 healthy pediatric controls. This suggests that increased amygdala volume in MDD could be due to plastic changes associated with increased blood flow and activation (Drevets et al. 1992, Drevets 2000, Frodl et al. 2002a, Sheline et al. 2001, Thomas et al. 2001).

It should be noted that Rosso et al. (2005) found significant reductions of left and right amygdalar volumes in patients with MDD in a recent investigation of 20 children and adolescents with MDD vs. 24 healthy comparison subjects. Right or left hippocampal volumes were not significantly different between pediatric patients with MDD and healthy controls. Discrepant findings among studies could relate to many factors, e.g., differences in study methodology, acquisition and analysis. This sample included predominantly female patients with MDD (17 of 20). Prior investigations in adult females with MDD have found reduced amygdala volumes (Sheline et al. 1996, Sheline et al. 1999, Hastings et al. 2004). Some of the patients studied by Rosso et al. (2005) received psychotropic medication, but all were medication free for at least 3 months prior to the MRI study. There may also be differences between familial and nonfamilial patients with MDD. Recent investigation in our laboratory by MacMaster and colleagues (unpublished data) found that increased amygdala volume and reduced hippocampal volume is more pronounced in familial patients with MDD than in

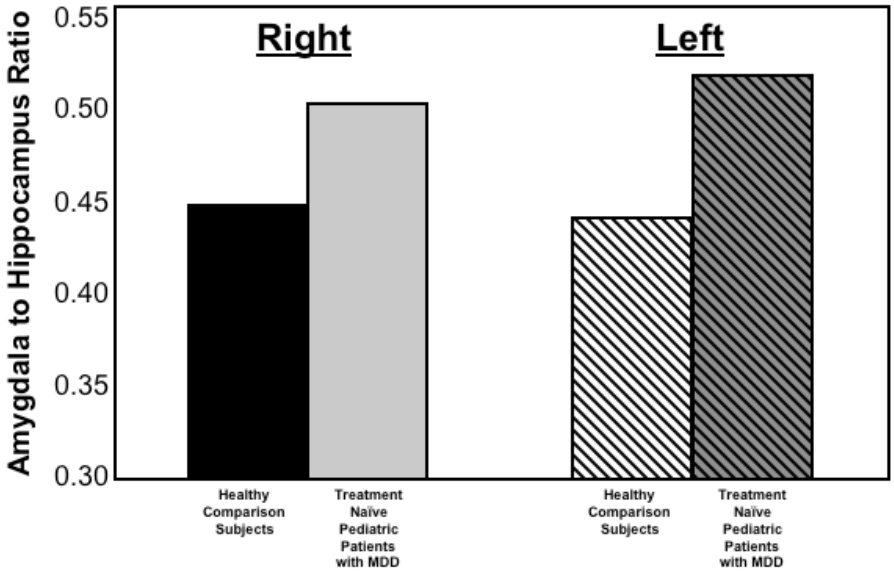


Figure 3. *Left and right amygdala/hippocampal volume ratios in healthy comparison subjects and MDD patients. MDD = major depressive disorder. Adapted from MacMillan et al. 2003*

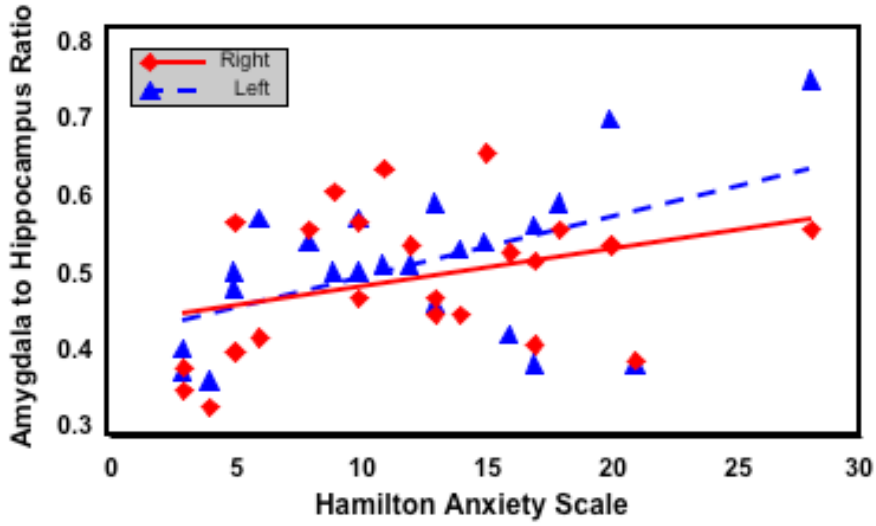


Figure 4. *Left and right amygdala/hippocampal volume ratios as a function of severity of anxiety as measured by the Hamilton Anxiety Scale in pediatric MDD patients. Note the correlation between left amygdala/hippocampal ratios and severity of anxiety in MDD patients and a trend between right amygdala/hippocampal ratios and severity of anxiety. Adapted from MacMillan et al. 2003*

nonfamilial patients with MDD. Clearly, this warrants further investigation.

Pituitary

One of the most replicated findings in biological psychiatry is hyperactivity of the limbic hypothalamic-pituitary adrenal (LHPA) axis in unmedicated patients with MDD (Nemeroff 1998). Healthy subjects at high familial risk for MDD demonstrate increased LHPA activity (Holsboer et al. 1995, Birmaher et al. 1997, Birmaher et al. 2000, Rao et al. 1996, Franz et al. 1995). Changes in endocrine activity are associated with changes in pituitary morphology (Gonzalez et al. 1988, Dinc et al. 1998). There are normative gender differ-

ences in the size of the pituitary with females having larger pituitary glands than males (Takano et al. 1999, MacMaster and Kusumakar 2004b).

Krishnan et al.(1991) reported larger pituitary size in elderly patients with MDD. MacMaster and Kusumakar (2004a) found larger pituitary gland volume in pediatric patients with MDD compared to healthy controls. Male patients with MDD demonstrated the most pronounced increase. More recently, MacMaster et al.(submitted) conducted volumetric MRI studies in 35 psychotropic-naïve pediatric patients with MDD (15 males, 20 females) 8-17 years of age and 35 age and sex-matched controls. Males with MDD had significantly larger pituitary volumes (19% larger) than male healthy controls. Pituitary volume did not differ significantly between females with MDD and controls. Nonfamilial male patients with MDD had significantly larger pituitary volumes (35%) than healthy controls and tended to have larger pituitary volumes than male patients with familial MDD (27%).

Neurochemistry

Pharmacologic studies still provide the most compelling evidence for a serotonergic role in pediatric MDD (Emslie et al. 1997, Emslie et al. 2002, TADS 2004). To date, fluoxetine is the only FDA approved antidepressant for depressed youth. Although meta-analyses of antidepressant trials for pediatric MDD tell a mixed story (Whittington et al. 2004, Vitiello and Swedo 2004, Brent 2004), SSRI's are currently the only medications in which some trials have demonstrated superiority to placebo. In child and adolescent MDD, tricyclic antidepressants are not superior to placebo (Ryan and Varma 1998).

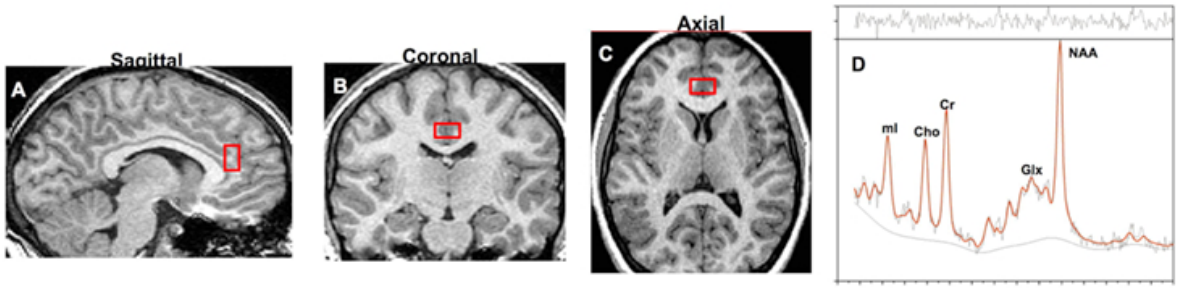
The serotonin hypothesis of MDD proposes that a deficit in serotonergic neurotransmission may result in vulnerability to MDD (Coppen 1967, Stahl 1998, Ressler and Nemeroff 2000, Maes and Meltzer 1995). Platelet and cerebrospinal fluid (CSF) studies of serotonin have reported alterations in pediatric and adult MDD patients compared to controls (Perez et al. 1998, Sallee et al. 1998, Figueras et al. 1999), although contradictory reports exist (Gomez-Gil et al. 2002). These studies, however, provide only a very peripheral window into brain chemistry. New advances in positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) provide unprecedented opportunities for obtaining an in vivo, noninvasive 'brain biopsy' of neurochemistry in patients with MDD. While PET allows for the measurement of serotonin synthesis and receptor function, its putative ionizing radiation risks make it less feasible for pediatric populations. While MRS does not permit direct measurement of serotonin, it can measure several neurochemical compounds that may be especially relevant to the pathophysiology of MDD.

Glutamate

There is increasing focus on the role of glutamate in the pathogenesis and treatment response of MDD (Sanacora et al. 2004; Zarate et al. 2002, 2003, 2004; Sanacora et al. 2003). Proton magnetic resonance spectroscopy (1H MRS) can measure glutamate and glutamine (Glx). Investigation demonstrating the antidepressant effects of agents targeting glutamatergic activity add to a growing body of evidence that altered glutamate concentrations may have particular clinical relevance. MDD is associated with regional reductions in anterior cingulated brain volume, number, size and density of glia and neurons, suggesting that MDD may be associated with alterations in structural plasticity and cellular resilience (Zarate et al. 2002, 2003, 2004).

Pre-clinical studies demonstrate that the caudate nucleus receives a massive innervation of glutamate so that ablation of the frontal cortex leads to a striking decrease in glutamate in the caudate nucleus (Becquet et al. 1990, Fonnum et al. 1981, Kim et al. 1977, Koller et al. 1984). Glutamate exerts a potent inhibitory effect on serotonin release in the caudate (Reisine et al. 1982). Prior investigation has also shown a potent presynaptic inhibition of serotonin release by cortico-striatal glutamate in the caudate nucleus (Becquet et al. 1990). El Mansari et al.(1995) has demonstrated that sustained administration of SSRI's enhanced the release of serotonin via desensitization of terminal serotonin autoreceptors in frontostriatal circuitry. Thus, SSRI treatment may lead to changes in serotonergic neurotransmission, which in turn, could influence frontostriatal glutamate projection as measured by changes in glutamate concentrations in the regions of interest, e.g., anterior cingulate cortex, basal ganglia. Investigation in pediatric patients with obsessive-compulsive disorder (OCD) demonstrating that SSRI treatment is associated with striking changes in caudate glutamatergic concentrations provides additional support for this hypothesis (Rosenberg et al. 2000).

Altamura et al. (1993, 1995) found medication-free adults with MDD to have abnormalities in plasma and platelet glutamate and glutamine. Cousins and Harper (1996) observed a decrease in Glx in two patients with secondary depression undergoing chemotherapy for breast cancer. Auer et al.(2000) observed significantly decreased Glx concentrations in 19 adults with MDD vs. 18 age-matched healthy volunteers. Anterior cingulate Glx reductions were most prominent in the most severely depressed patients. Parietal white matter Glx did not differ between groups. When fitting to individually quantify glutamate, Auer et al. (2000) showed significantly reduced anterior cingulate but not parietal white matter glutamate. The investigators were not able to individually quantify glutamine. There were also no significant differences observed in anterior cingulate or parietal white matter N-acetyl-aspartate (NAA), a putative neuronal marker (Birken and Oldendorf 1989), choline compounds (Cho), creatine/phosphocreatine (Cr) or myo-inositol (mI). Pfleiderer et al.(2003) confirmed and extended this finding of reduced anterior cingulate Glx in adults with MDD. There were no significant group differences in anterior cingulate NAA, Cho and Cr. However, there was a striking increase of Glx in 12 of the patients with MDD who responded to electroconvulsive therapy (ECT). After ECT, Glx levels were not significantly different from levels observed in healthy volunteers. Moreover, in the five patients who failed to respond to ECT, there was no increase in anterior cingulate Glx. However, in



Figures 5. *Voxel placement (A. Sagittal, B. Coronal, C. Axial; a 3 cc volume of interest) with LCModel fit (D) from the anterior cingulate cortex. NAA = N-acetyl-aspartate; Glx = glutamate/glutamine; Cr = creatine/phosphocreatine; Cho = choline compounds; mI = myo-inositol* (Adapted from Mirza Y, Tang J, Russel A, et al 2004). Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. *J Am Acad Child Adolesc Psychiatry* 43, 341-348

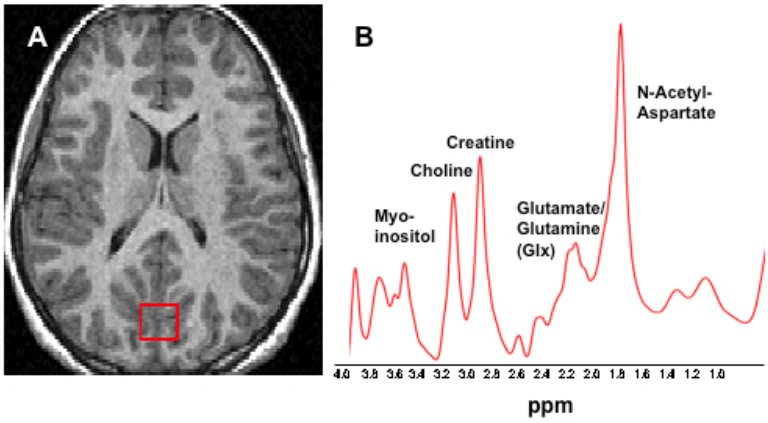
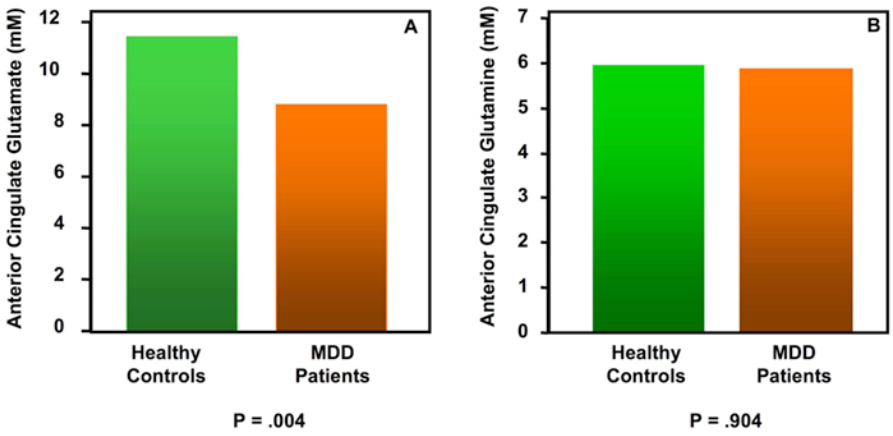


Figure 6. *Voxel placement (A. Axial; an 8 cc volume of interest) with LCModel fit (B) from the occipital lobe. NAA = N-acetyl-aspartate; Glx = glutamate/glutamine; Cr = creatine/phosphocreatine; Cho = choline compounds; mI = myo-inositol. Adapted from Mirza et al. 2004*



Figures 7. *Anterior cingulate glutamate concentrations in healthy comparison subjects compared with pediatric MDD patients (A). Glutamate concentrations are significantly lower in pediatric MDD patients. Anterior cingulate glutamine concentrations in healthy comparison subjects compared with pediatric MDD patients (B). Glutamine concentrations do not differ significantly between the two groups. MDD = major depressive disorder. Reprinted from Biological Psychiatry, 58, Rosenberg et al., Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study, 700-704, 2005, with permission from the Society for Biological Psychiatry*

three of the five non-responders when examined a third time after their depressive symptoms had remitted on combined ECT and antidepressant treatment, Glx increased to twice the non-response level. Contrast this with the finding that when measured a third time after their depression had remitted, responders demonstrated stable Glx levels.

Mirza et al.(2004) conducted a single voxel 1H MRS (1.5T study) from a 3 cc volume of interest in the anterior cingulate and 8 cc voxel in occipital cortex (Figures 5 and 6). Mirza et al.(2004) found a smaller Glx concentration in the anterior cingulate in pediatric MDD patients vs. controls. Reduction in anterior cingulate Glx was associated with increased severity of functional impairment. In contrast, occipital cortex Glx concentrations did not differ significantly between patients with MDD and controls. These spectra were subsequently analyzed using LCModel (Version 6.1-0) and LCMgui (Version 2.1-0) (Provencher 2001), with the basis set created from data acquired on the 1.5 Tesla General Electric Signa MRI scanner. The spectra were automatically fit following automatic Eddy-Current Correction. We performed fitting to individually quantify glutamate and glutamine. Anterior cingulate glutamate, but not glutamine, concentrations were significantly smaller in psychotropic-naïve pediatric patients with MDD (Rosenberg et al. 2005) (Figures 7). There were no significant differences in occipital cortex glutamate or glutamine concentrations between patients with MDD and controls.

These studies in pediatric patients with MDD provide new data about localized disturbances in anterior cingulate Glx neurotransmission without potentially confounding factors of psychotropic medications and longer illness duration. Decreased anterior cingulate glutamate in MDD may be consistent with prior investigations demonstrating reduced volume, perfusion, metabolism and serotonin synthesis in anterior cingulate cortex. Glutamate activity parallels brain glucose metabolism (Sibson et al. 1997). These results are also consistent with the recently proposed glutamate deficiency model of MDD (Pfleiderer et al. 2003). There is evidence; therefore, suggesting that anterior cingulate Glx levels are predominantly glutamate (Auer et al. 2000, Pouwels and Frahm 1998). GABA levels in the brain are much lower than glutamate and glutamine levels (about 1 mmol/kg brain tissue vs. 12-14 mmol/kg brain tissue). Nonetheless, there is general acknowledgement that at higher magnetic field strengths the individual subcomponents of the Glx resonance (e.g., glutamate, glutamine, GABA and relevant macromolecules) are best measured. There is an advantage to using clinical 1.5 Tesla MRI scanners in that the findings are more rapidly generalized to the many institutions and centers that have these MRI scanners.

Choline

The 1H MRS choline (Cho) signal contains diverse choline-containing compounds, such as phosphorylcholine, glycerophosphocholine and acetylcholine (Barker et al. 1994, Miller et al. 1996). Cho plays a critical role in signal transduction (Steingard et al. 2000). Charles et al.(1994) found increased basal ganglia Cho in psychotropic medication-free elderly patients with MDD. The elevated Cho levels decreased

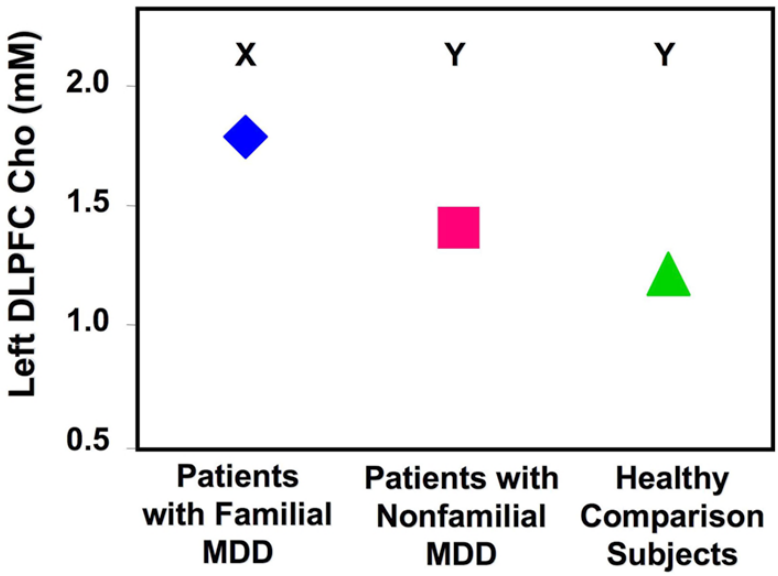


Figure 8. *Comparison of psychotropic-naïve pediatric patients with familial MDD, nonfamilial MDD and healthy pediatric controls. Cho = choline containing compounds; DLPFC = dorsolateral prefrontal cortex; mM = millimolar*

in patients with MDD after antidepressant treatment. Hamakawa et al.(1998) reported increased basal ganglia Cho in bipolar depressed patients with a non-significant trend for increased Cho also observed in adult patients with MDD. Renshaw et al.(1997), however, observed reduced left basal ganglia Cho levels in young adult patients with MDD that were most notable in SSRI treatment responders. In a follow-up investigation, Sonawalla et al.(1999) found that basal ganglia Cho may serve as a biomarker of response to antidepressant treatment. Moore et al.(2000) observed increased Cho levels in the anterior cingulate cortex of adult patients with bipolar depression. Severity of depression positively correlated with increased Cho. Antidepressant treatment resulted in lower Cho levels.

Left hemispheric lesions have been more associated with depression, whereas right hemispheric lesions may be more associated with mania (Soares and Mann 1997b). Indeed, two recent 1H MRS investigations in pediatric patients with MDD have further implicated left prefrontal cortex in the pathogenesis of this illness. Steingard et al.(2000) noted increased orbital frontal Cho levels in adolescent patients with MDD compared to healthy controls. Increased orbital Cho levels were most prominent in adolescent patients with familial MDD vs. both nonfamilial patients with MDD and healthy controls (Personal Communication, Dr. Perry Renshaw). Farchione et al.(2002) also found increased left but not right dorsolateral prefrontal cortical Cho concentrations in psychotropic-naïve pediatric patients with MDD vs. age and sex-matched healthy comparison subjects. These increased left dorsolateral prefrontal Cho concentrations in the patients with MDD persisted after controlling for severity of anxiety. In familial patients with MDD compared to both nonfamilial pediatric patients with MDD and healthy pediatric controls, left dorsolateral prefrontal cortex Cho concentrations were increased (see Figure 8). Abnormalities in Cho as measured by 1H MRS may result from alterations in signal transduction involving phosphotidylcholine second messenger cascades and may be associated with changes in glucose metabolism and neuroendocrine function (Steingard et al. 2000, Farchione et al. 2002). Given reports that Cho alterations may be reversible in adults with MDD (Charles et al. 1994), Cho alterations in pediatric patients with MDD may represent potential treatment targets. Since 1H MRS is noninvasive, longitudinal assessments pre-post treatment are warranted.

Creatine/Phosphocreatine

The 1H MRS creatine/phosphocreatine (Cr) peak includes very high concentrations of the high-energy phosphate, phosphocreatine, in the brain. Mirza et al.(2004) observed reduced anterior cingulate Cr concentrations in psychotropic-naïve pediatric patients with MDD. This could reflect reduced energy utilization in anterior cingulate cortex. This may also be consistent with findings of decreased perfusion and metabolism in anterior cingulate cortex in patients with MDD (Bench et al. 1995, Ebert and Ebmeier 1996, Goodwin 1996, Mayberg et al. 1997). 31 Phosphorous MRS may also be helpful in better elucidating the role of Cr in the pathophysiology of MDD as it can discriminate the individual components of the Cr resonance.

Conclusions

Taken together, this research in pediatric MDD illustrates the promise of integrating assessment, treatment and neurobiological studies designed to elucidate markers of illness and treatment response. There has been a striking paucity of neuroimaging studies in pediatric MDD. Given its enormous public health importance and the need for enhanced diagnostic rigor and new treatment development, there is a critical need for studies targeting the development, evaluation and dissemination of new moderating (present at baseline) and mediating (changing with treatment) biomarkers of MDD. Such projects must emphasize the integration and translation of MRI measurement as it relates to neurodiagnostic assessment and treatment development for pediatric MDD. Such a series of studies may begin to lay the groundwork to address the clinically relevant question, "Which treatments for which depressed child with which set of sub-grouping characteristics using relevant biomarkers (e.g., SSRI, psychotherapy or their combination for patients with specific functional neuroanatomic and neurochemical patterns)." Exciting times lie ahead in our efforts to tackle the mechanisms involved in MDD and its treatment response.

Acknowledgments: This work was supported in part by the State of Michigan Joe F. Young Sr. Psychiatric Research and Training Program, grants from the National Institute of Mental Health (MH65122, MH59299, MH02037), National Alliance for Research on Schizophrenia and Depression, and the Miriam L. Hamburger Endowed Chair of Child Psychiatry at Children's Hospital of Michigan and Wayne State University.

References:

Aggleton JP (1992). *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. Wiley-Liss, New York.

Altamura CA, Mauri MC, Ferrara A, et al (1993). Plasma and platelet excitatory amino acids in psychiatric disorders. *Am J Psychiatry* 150, 1731–1733.

Altamura CA, Maes M, Dai J, et al (1995). Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *Eur Neuropsychopharmacol* S, 71–75.

Angold A, Messer SC, Stangl D, et al (1998). Perceived parental burden and service use for child and adolescent psychiatric disorders. *Am J Public Health* 88, 75-80.

Arias E, MacDorman MF, Strobino DM, et al (2003). Annual summary of vital statistics—2002. *Pediatrics* 112, 1215-1230.

Auer DP, Putz B, Kraft E et al (2000). Reduced glutamate in the anterior cingulate cortex in depression: An in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 47, 305-313.

Barker P, Breiter S, Soher B, et al (1994). Quantitative proton spectroscopy of canine brain: In vivo and in vitro correlations. *Magn Reson Med* 32, 157–163.

Becquet D, Faudon M, Hery F (1990). In vivo evidence for an inhibitory glutamatergic control of serotonin release in the

cat caudate nucleus: Involvement of GABA neurons. *Brain Res* 519, 82-88.

Bench CJ, Frackowiak RS, Dolan RJ (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychol Med* 25, 247-261.

Birken DL, Oldendorf WH (1989). N-acetyl-L-aspartic acid: A literature review of a compound prominent in 1H-NMR spectroscopic studies of brain (Review). *Neurosci Biobehavior Rev* 13, 23-31.

Birmaher B, Ryan ND, Williamson DE, et al (1996a). Childhood and adolescent depression: a review of the past 10 years. Part II. *J Am Acad Child Adolesc Psychiatry* 35, 12, 1575-83.

Birmaher B, Ryan ND, Williamson DE, et al (1996b). Childhood and Adolescent Depression: A review of the past 10 years. Part I. *J Am Acad Child Adolesc Psychiatry* 35, 427-1439.

Birmaher B, Kaufman J, Brent DA, et al (1997). Neuroendocrine response to 5-hydroxy-L-tryptophan in prepubertal children at high risk of major depressive disorder. *Arch Gen Psychiatry* 54, 1113-9.

Birmaher B, Dahl RE, Williamson DE, et al (2000). Growth hormone secretion in children and adolescents at high risk for major depressive disorder. *Arch Gen Psychiatry* 57, 867-72.

Botteron KN, Raichle ME, Drevets WC, et al (2002). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry* 51, 342-344.

Bremner JD, Narayan M, Anderson ER, et al (2000). Hippocampal volume reduction in major depression. *Am J Psychiatry* 157, 1, 115-8.

Brent DA, Moritz G, Bridge J, et al (1996). The impact of adolescent suicide on siblings and parents: A longitudinal follow-up. *Suicide Life Threat Behav* 26, 253-259.

Brent DA, Birmaher B (2004). British warnings on SSRI's questioned. *J Am Acad Child Adolesc Psychiatry* [letter] 43, 379-380.

Brody Al, Saxena S, Stoessel P, et al (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: Preliminary findings. *Arch Gen Psychiatry* 158, 631-640.

Charles HC, Lazeyras F, Krishnan KR, et al (1994). Brain choline in depression: In vivo detection of potential pharmacodynamic effects of antidepressant therapy using hydrogen localized spectroscopy. *Prog Neuropsychopharmacol Biol Psychiatry* 18, 1121–1127.

Coppen A (1967). The biochemistry of affective disorders. *Br J Psychiatry* 113, 1237-1264.

Cousins JP, Harper G (1996). Neurobiochemical changes from Taxol/Neupogen chemotherapy for metastatic breast carcinoma corresponds with suicidal depression. *Cancer Lett* 110, 163–167.

Davidson, RJ. Irwin, W (1999). The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci* 3, 11-21.

Davis M (1994). The role of the amygdala in emotional learning. *Int Rev Neurobio* 36, 225-266.

De Bellis MD, Casey BJ, Dahl RE, et al (2000). A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biol Psychiatry* 48, 51-57.

Dinc H, Esen F, Demirci A, et al (1998). Pituitary dimensions and volume measurements in pregnancy and post partum, MR assessment. *Acta Radiol* 39, 64-9.

Drevets WC, Videen TO, Price JL, et al (1992). A functional anatomical study of unipolar depression. *J Neurosci* 12, 3628-3641.

Drevets WC, Price JL, Simpson JR, et al (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386, 827.

Drevets WC (1998). Functional neuroimaging studies of depression: The anatomy of melancholia. *Annu Rev Med* 49, 341-361.

Drevets WC (2000). Neuroimaging studies of mood disorders. *Biol Psychiatry* 48, 813.

Ebert D, Ebmeier KP (1996). The role of the cingulate gyrus in depression-from functional anatomy to neurochemistry. *Biol Psychiatry* 39, 1044-1050.

El Mansari M, Bouchard C, Blier P (1995). Alteration of serotonin release in the guinea pig orbito-frontal cortex by selective serotonin reuptake inhibitors. Relevance to treatment of obsessive-compulsive disorder. *Neuropsychopharmacology* 13, 117-127.

Emslie GJ, Rush AJ, Weinberg WA, et al (1997). A double blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 4, 1031-1037.

Emslie GJ, Heiligenstein JH, Wagner KD, et al (2002). Fluoxetine for acute treatment of depression in children and adolescents: A placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41, 1205-1215.

Essau C, Dobson K (1999). Epidemiology of depressive disorders. *In* Essau C, Peterman F (Eds) *Depressive disorders in children and adolescents: epidemiology, course and treatment*, Aronson, Northvale, NJ.

Farchione TR, Moore GJ, Rosenberg DR (2002). Proton magnetic resonance spectroscopic imaging in pediatric major depression. *Biol Psychiatry* 52, 86-92.

Figueras G, Perez V, San Martino O, et al (1999). Pretreatment platelet 5-HT concentration predicts the short-term response to paroxetine in major depression. *Biol Psychiatry* 46, 518-524.

Fonnum F, Storm-Mathisen J, Divac I (1981). Biochemical evidence for glutamate as neurotransmitter in corticostriatal and corticothalamic fibers in rat brain. *Neuroscience* 6, 863-873.

Franz B, Kupfer DJ, Miewald JM, et al (1995). Growth hormone secretion timing in depression: Clinical outcome comparisons. *Biol Psychiatry* 38, 720-9.

Frodl T, Meisenzahl E, Zetzsche T, et al (2002a). Enlargement of the amygdala in patients with a first episode of major depression. *Biol Psychiatry* 51, 9, 708-14.

Frodl T, Meisenzahl EM, Zetzsche T, et al (2003). Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. *Biol Psychiatry* 53, 4, 338-44.

Frodl T, Meisenzahl E, Zetzsche T, et al (2002b). Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry* 159, 1112-1118.

Giedd, A.C. Vaituzis, S.D. Hamburger, N, et al (1996). Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development ages 4–18 years. *J Comp Neurol* 366, 223–230.

Goldapple K, Segal Z, Garson C, et al (2004). Modulation of cortical-limbic pathways in major depression. *Arch Gen Psychiatry* 61, 34-41.

Gomez-Gil E, Gasto C, Diaz-Ricart M, et al (2002). Platelet 5-HT2A receptor-mediated induction of aggregation is not altered in major depression. *Hum Psychopharmacol* 17, 419-424.

Gonzalez JG, Elizondo G, Saldivar D, et al (1988). Pituitary gland growth during normal pregnancy: An in vivo study using magnetic resonance imaging. *Am J Med* 85, 217-20.

Goodwin GM (1996). Functional imaging, affective disorder and dementia. *Br Med Bull* 52, 495-512.

Halgren E, Walter RD, Cherlow DG, et al (1978). Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. *Brain* 10, 83-117.

Hamakawa H, Kato T, Murashita J, et al (1998). Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. *Eur Arch Psychiatry Clin Neurosci* 248, 53–58.

Hastings, R.V. Parsey, M.A. Oquendo, et al (2004). Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 29, 952–959.

Holsboer F, Lauer CJ, Schreiber W, et al (1995). Altered hypothalamic-pituitary-adrenocortical regulation in healthy

subjects at high familial risk for affective disorders. *Neuroendocrinology* 62, 340-7.
Hyman SE (2000). The millennium of mind, brain, and behavior. *Arch Gen Psychiatry* 57, 88-89.
Kaufman MJ, Henry ME, Frederick B, et al (2003). Selective serotonin reuptake inhibitor discontinuation syndrome is associated with a rostral anterior cingulate choline metabolite decrease: A proton magnetic resonance spectroscopic imaging study. *Biol Psychiatry* 54, 534-539.
Kennedy SH, Evans KR, Kruger S, et al (2001). Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am J Psychiatry* 158, 899-905.
Kessler RC, McGonagall KA, Nelson CB, et al (1994). Sex and depression in the national comorbidity Survey II: Cohort effects. *J Affect disorder* 30, 15-26.
Kessler RC, Avenevoli S, Merikangas KR (2001). Mood disorders in children and adolescents: An epidemiologic perspective. *Biol Psychiatry* 49, 1002-1014.
Kim JS, Hasller R, Hau P, et al (1977). Effect of frontal cortex ablation on striatal glutamic acid level in rat. *Brain Res* 132, 370-374.
Koller KJ, Zaczek R, Coyle JT (1984). N-acetyl-aspartyl-glutamate: Regional levels in rat brain and the effects of brain lesions as determined by a new HPLC method. *J Neurochem* 43, 1136-1142.
Krishnan KR, Doraiswamy PM, Lurie SN, et al (1991). Pituitary size in depression. *J Clin Endocrinol Metab* 72, 256-9.
Lane RD, Reiman EM, Bradley MM, et al (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 35, 1437-1444.
LeDoux JE (1996). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. Simon & Schuster, New York.
Lewinsohn PM, Fenn DS, Stanton AK, et al (1986). Relation of age at onset to duration of episode in unipolar depression. *Psychol Aging* 1, 63-68.
Lewinsohn PM, Hops H, Roberts RE, et al (1993a). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *J Abnorm Psychol* 102, 133-144.
Lewinsohn PM, Rohde P, Seeley JR (1993b). Psychosocial characteristics of adolescents with a history of suicide attempt. *J Am Acad Child Adolesc Psychiatry* 32, 60-68.
MacMaster FP, Kusumakar V (2004a). Hippocampal volume in early onset depression. *BMC Med* 2, 2.
MacMaster FP, Kusumakar V (2004b). MRI study of the pituitary gland in adolescent depression. *J Psychiar Res* 38, 231-236.
MacMaster FP, Russell A, Mirza Y, et al (In Press). Pituitary Volume in treatment-naïve pediatric major depressive disorder. *Biol Psychiatry*.
MacMillan PR, Szeszko GJ, Moore R, et al (2003). Increased amygdala hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *J Child Adolesc Psychopharmacol* 13, 65-73.
Maes M, Meltzer HY (1995). The serotonin hypothesis of major depression. In Bloom F, Kupfer D (Eds) *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, New York, NY.
Martin SD, Martin E, Rai SS, et al (2001). Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: Preliminary findings. *Arch Gen Psychiatry* 58, 641-648.
Mayberg HS (2002). Modulating limbic-cortical circuits in depression: Targets of antidepressant treatments. *Semin Clin Neuropsychiatry* 7, 255-268.
Mayberg HS, Brannan SK, Mahurin RK et al (1997). Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8, 1057–1061.
Miller BL, Chang L, Booth R, et al (1996). In vivo 1H MRS choline: Correlation with in vitro chemistry/histology. *Life Sci* 58, 1929-1935.
Mirza Y, Tang J, Russell A, et al (2004). Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. *J Am Acad Child Adolesc Psychiatry* 43, 341-348.
Moore CM, Breeze JL, Gruber SA, et al (2000). Choline, myo-inositol and mood in bipolar disorder: A proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. *Bipolar Disord* 2, 207-216.
Nemeroff CB (1998). The neurobiology of depression. *Sci Am* 278, 42-9.
Nolan CL, Moore GJ, Madden R, et al (2002). Prefrontal cortical volume in childhood-onset major depression: Preliminary findings. *Arch Gen Psychiatry* 59, 2, 173-9.
Papez JW (1937). A proposed mechanism of emotion. *Arch Neurol Psychiatry* 38, 725-743.
Perez V, Be N, Celada P, et al (1998). Relationship between blood serotonergic variables, melancholic traits, and response to antidepressant treatments. *J Clin Psychopharmacol* 18, 222-230.
Pfleiderer B, Michael N, Erfurth A, et al (2003). Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. *Psychiatry Res* 122, 185-192.
Pfluger, S. Weil, S. Weis, et al (1999). Normative volumetric data of the developing hippocampus in children based on magnetic resonance imaging. *Epilepsia* 40, 4, 414–423.
Phelps EA, Anderson AK (1997). Emotional memory: What does the amygdala do? *Curr Biol* 7, R311-R314.
Pine DS, Cohen E, Cohen P, et al (1999). Adolescent depressive symptoms as predictors of adult depression: Moodiness or mood disorder? *Am J Psychiatry* 156, 133-135.
Pine DS, Cohen P, Brook J (2001). Adolescent fears as predictors of depression. *Biol Psychiatry* 50, 9, 721-4.
Pouwels PJW, Frahm J (1998). Regional metabolite concentration in human brain as determined by quantitative localized proton MRS. *Magn Reson Med* 39, 53-60.
Provencher (2001). Automatic quantitation of localized in vivo H-1 spectra with LCModel. *NMR in Biomedicine* 14, 260-264.
Rao U, Dahl RE, Ryan ND, et al (1996). The relationship between longitudinal clinical course and sleep and cortisol changes in adolescent depression. *Biol Psychiatry* 40, 474-84.
Reisine T, Soubrie P, Artaud F, et al (1982). Application of L-glutamic acid and substance P to the substantia nigra modulates in vivo [3H] serotonin release in the basal ganglia of the cat. *Brain Res* 236, 317-327.
Renshaw PF, Lafer B, Babb SM, et al (1997). Basal ganglia choline levels in depression and response to fluoxetine treatment: An in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 41, 837-843.
Ressler KJ, Nemeroff CB (2000). Role of the serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress Anxiety* 12, 2-19.
Rosenberg DR, MacMaster FP, Keshavan MS, et al (2000). Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. *J Am Acad Adolesc Psychiatry* 39, 1096-1103.
Rosenberg DR, MacMaster FP, Mirza Y, et al (2005). Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. *Biol Psychiatry* 58, 700-704.
Rosso IM, Cintron CM, Steingard RJ, et al (2005). Amygdala and hippocampus volumes in pediatric major depression. *Biol Psychiatry* 57, 1, 21-6.
Ryan ND, Varma D (1998). Child and adolescent mood disorders—experience with serotonin-based therapies. *Biol Psychiatry* 44, 5, 336-40.
Sallee FR, Hilal R, Dougherty D, et al (1998). Platelet serotonin transporter in depressed children and adolescents: 3H-paroxetine platelet binding before and after sertraline. *J Am Acad Child Adolesc Psychiatry* 37, 777-784.

Sanacora G, Kendell SF, Fenton L, et al (2004). Riluzole augmentation for treatment-resistant depression. Am *J Psychiatry* [letter] 161, 2132.

Sanacora G, Rothman DL, Mason G, et al (2003). Clinical studies implementing glutamate neurotransmission in mood disorders. *Ann N Y Acad Sci* 1003, 292-308.

Sheline YI, Wang PW, Gado MH, et al (1996). Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 93, 9, 3908-13.

Sheline YI, Sanghavi M, Mintun MA, et al (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19, 12, 5034-43.

Sheline YI, Barch DM, Donnelly JM, et al (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biol Psychiatry* 50, 9, 651-8.

Sibson NR, Dhankhar A, Mason GF, et al (1997). In vivo 13CNMR measurements of cerebral glutamine synthesis as evidence for glutamate-glutamine cycling. *Proc Natl Acad Sci USA* 94, 2699-2704.

Soares JC, Mann JJ (1997a). The functional neuroanatomy of mood disorders. *J Psychiatr Res* 31, 4, 393-432.

Soares JC, Mann JJ (1997b). The anatomy of mood disorders—review of structural neuroimaging studies. *Biol Psychiatry* 41, 86–106.

Sonawalla S, Parikh R, Parikh F (1999). Compounds containing cytosolic choline in the basal ganglia: A potential biological marker of true drug response to fluoxetine. *Am J Psychiatry* 156, 1638–1640.

Stahl SM (1998). Mechanism of action of serotonin selective reuptake inhibitors: Serotonin receptors and pathways mediate therapeutic effects. *J Affect Disorder* 51, 215-235.

Steffens DC, Byrum CE, McQuoid DR, et al (2000). Hippocampal volume in geriatric depression. *Biol Psychiatry* 48, 4, 301-9.

Steingard RJ, Renshaw PF, Hennen J, et al (2002). Smaller Frontal Lobe White Matter Volumes in Depressed Adolescents. *Biol Psychiatry* 52, 413.

Steingard RJ, Yurgelun-Todd DA, Hennen J, et al (2000). Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. *Biol Psychiatry* 48, 1053–1061.

Takano K, Utsunomiya H, Ono H, et al (1999). Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. *AJNR Am J Neuroradiol* 20, 312-5.

Tebartz van Elst L, Woermann F, Lemieux L, et al (2000). Increased amygdala volumes in female and depressed humans: A quantitative magnetic resonance imaging study. *Neurosci Lett* 281, 103-106.

Thomas KM, Drevets WC, Dahl RE, et al (2001). Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry* 58, 11, 1057-63.

The Treatment for Adolescents with Depression Study [TADS] Team (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA* 292, 807-820.

Vitiello B, Swedo S (2004). Antidepressant medications in children. *N Engl J Med* 350, 1489-1491.

Weissman MM, Wolk S, Goldstein RB, et al (1999). Depressed adolescents grown up. *JAMA* 281, 1707-1713.

Whittington CJ, Kendall T, Fonagy P, et al (2004). Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet* 363, 1341-1345.

Yurgelun-Todd, Killgore WD, Cintron CB (2003). Cognitive correlates of medial temporal lobe development across adolescence: A magnetic resonance imaging study. *Percept Mot Skills* 96, 3–17.

Zarate CA, Quiroz J, Sporn J, et al (2002). Modulators of the glutamatergic system: A new class of antidepressants. *Biol Psychiatry* 353, 707-742.

Zarate CA, Du J, Quiroz J, et al (2003). Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: Role of the glutamatergic system. *Ann NY Acad Sci* 1003, 273-291.

Zarate CA, Payne JL, Quiroz J, et al (2004). An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 161, 171-174.