Amygdala and Hippocampal Volumes in Familial Early Onset Major Depressive Disorder

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Background: Abnormalities in the amygdala and hippocampus have been implicated in the pathogenesis of major depressive disorder (MDD). To our knowledge, no prior study has examined amygdala-hippocampus anatomy in pediatric patients with familial MDD (at least one first degree relative with MDD).

Methods: Thirty-two psychotropic-naive patients with familial MDD, aged 8–21 years (12 males and 20 females), and 35 group-matched healthy participants (13 males and 22 females) underwent volumetric magnetic resonance imaging in order to evaluate hippocampal and amygdala volumes.

Results: Patients with familial MDD had significantly smaller left hippocampal ($p = .007$, effect size [d] = .44) and right hippocampal volumes ($p = .025$, d = .33) than controls. No differences were noted in amygdala volumes between groups (right: $p > .05$, left: $p > .05$). No correlations between hippocampal or amygdala volumes and demographic or clinical variables were noted.

Conclusions: Reduced hippocampal volume may be suggestive of a risk factor for developing MDD.

Key Words: Adolescents, amygdala, depression, familial, hippocampus, magnetic resonance imaging

Major depressive disorder (MDD) is a common, debilitating and often severe illness with frequent onset in childhood and adolescence. The lifetime prevalence of pediatric MDD is 15 to 20%, consistent with rates reported in adult MDD samples (1). Studies of pediatric patients with MDD may minimize potential confounds such as treatment intervention and illness duration. Investigations of pediatric MDD may also clarify potential neurodevelopmental abnormalities related to the pathogenesis of the disease.

Temporal-limbic structures, such as the amygdala and hippocampus, are critical in regulating emotion (2). Dysfunction in the hippocampus and amygdala has been hypothesized to be involved in causing depressive symptoms. Decreased hippocampal volumes have been reported in adults with MDD compared to healthy controls (3–6). Increased amygdala volume has also been observed in first episode adults with MDD as compared to healthy controls (7). Frodl *et al.* (8) extended this finding by noting significantly larger amygdala volumes in patients with a first episode of MDD compared to patients with recurrent MDD and healthy controls. Enlarged amygdala volumes were found in patients with temporal lobe epilepsy and comorbid depression as compared to patients with temporal lobe epilepsy without comorbid depression and healthy controls (9). MacMillan *et al.* (10) reported increased amygdala to hippocampal volume ratios in psychotropic-naive pediatric patients with MDD compared to age and sex-matched pediatric controls. While amygdala volumes tended to be larger and hippocampal volumes smaller in pediatric patients with MDD versus controls, these differences were not statistically significant. MacMaster and Kusumakar (11) did, however, observe significant reductions in hippocampal volume in adolescents with MDD compared with age and sex matched controls. In contrast, Rosso *et al.* (12) reported significantly decreased amygdala volume with no differences in hippocampal volume in pediatric patients with MDD versus healthy pediatric controls. Methodological differences in measurements of the regions of interest and sample characteristics could account for varying/discrepant results in the literature, e.g, psychotropic-naive, more comorbid anxiety disorders in the MacMillan *et al.* (10) investigation, while in the Rosso *et al.* (12) report, some patients were on medication and there was less comorbid anxiety. Re-analysis of the 23 pediatric patients with MDD reported in the MacMillan *et al.* (10) investigation suggested that volumetric alterations were more prominent in the 13 pediatric patients with familial MDD (e.g, patients with at least one first degree relative with MDD) compared to the 10 pediatric patients with nonfamilial MDD (no obvious family history of mood disorder; unpublished observation). Prior investigation in the subgenual region of the prefrontal cortex has also demonstrated volumetric alterations that are most prominent in patients with familial MDD as compared to both patients with nonfamilial MDD and healthy controls (13–16).

Interestingly, prefrontal-limbic alterations have been noted in other affective disorders. In first-episode bipolar disorder, Rosso *et al.* (17) noted smaller amygdala volume as compared to controls, similar to what was noted in MDD (12). Chang *et al.* (18) found smaller amygdala volumes but no difference in hippocampal volume between pediatric bipolar subjects and controls. Using voxel based morphometry, Dickstein *et al.* (19) noted reductions in amygdala and left dorsolateral prefrontal cortex volumes in pediatric bipolar disorder as compared to controls.

Twenty to 46% of MDD patients have a first degree relative with the disorder. An inverse relationship has been noted between age of onset of MDD and the density of familial loading of the disease (20,21). The amygdala and hippocampus undergo striking maturational changes during childhood and adolescence

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(22–24). The current volumetric magnetic resonance imaging (MRI) investigation was conducted to evaluate amygdala and hippocampal volume in a large sample of psychotropic-naive pediatric patients with familial MDD. We predicted reduced hippocampal volumes (3–6,11) and increased amygdala volumes (7,8) in pediatric patients with familial MDD compared to matched healthy volunteers. A secondary analysis used the subjects not included in our previous report (10) to determine if our results held with just the novel sample.

Methods and Materials

Subjects

Sixteen right hand–dominant (25), psychotropic-naive patients with MDD, aged 8 to 21 years (7 males, 9 females), and 17 healthy controls (7 males, 10 females) were matched group-wise for age. These subjects have not been previously reported. For the larger analysis, an additional 32 subjects, reported previously (10,26) were added (controls: 6 males and 12 females; MDD patients: 6 males and 12 females) (see Table 1 for summary). Participants were recruited after being referred to the Pediatric Mood and Anxiety Disorders Program at Wayne State University and the Children's Hospital of Michigan. Controls were recruited via advertisement. Patients and controls were paid an honorarium for their participation in this clinical research study. The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (27) was administered to all participants and their parent(s) by the child psychologists and psychiatrists. A board-certified pediatric psychiatrist (D.R.R. or Y.M.) reviewed all clinical information and confirmed DSM-IV (28) diagnostic criteria as well as associated medical or neurologic conditions. Exclusion criteria included lifetime history of psychosis, bipolar disorder, obsessive-compulsive disorder, anorexia or bulimia nervosa, posttraumatic stress disorder, substance abuse or dependence, Tourette's syndrome or other tic-related conditions, autism, mental retardation or learning disabilities, or significant medical or neurologic conditions. As determined by Family History–Research Diagnostic Criteria (29), all patients with MDD had at least one first-degree relative with MDD. No patients had a first-degree relative with bipolar disorder, using the same criteria. Controls had no history of psychiatric illness and no first degree relative with a DSM-IV (28) Axis I disorder. Written informed consent was obtained from legal guardians and written assent was obtained from all participants prior to initiating the study in compliance with the regulations of the Wayne State University Human Investigation Committee.

Assessments

Depressive symptom severity was measured using the Childhood Depression Rating Scale-Revised (CDRS-R) (30). All patients had a CDRS-R score of at least 40, which is indicative of significant dysfunction. Severity of anxiety was assessed with the Hamilton Anxiety Rating Scale (HAMA, mean ± SD score, new subjects: 14.50 ± 7.24; old subjects: 14.25 ± 6.09; overall: 14.38 ± 6.58) (31). A score of 14 or higher is considered clinically significant (32) and 18 (56%) of the MDD patients scored 14 or greater. Duration of illness was also recorded.

Magnetic Resonance Imaging Acquisition and Analysis

Magnetic resonance imaging studies were conducted with a 1.5-Tesla (version 5.7; GE Signa; General Electric, Milwaukee, Wisconsin) magnetic resonance system (General Electric). Image acquisition and analysis are described in detail in our prior reports (10,26,33–37). Briefly, a sagittal scout series was obtained to determine image quality and clarity. A three-dimensional spoiled gradient echo-pulse sequence obtained 124, 1.5-mm-thick coronal contiguous slices through the entire brain, perpendicular to the anterior commissure–posterior commissure line (time-to-echo = 5 msec; repetition time = 25 msec; acquisition matrix = 256 × 256 pixels; field of view = 24 cm; and flip angle = 10°). All MRI scans were reviewed to rule out clinically significant abnormalities. Images were exported from the MRI unit to a computer workstation (MacIntosh Personal Computer; Apple Computer, Cupertino, California).

Anatomical boundaries (detailed definitions are available on request) were determined from neuroanatomical atlases (38). Descriptions of the measurement methods have been detailed previously for intracranial volume (33), amygdala and hippocampus (10,35). Briefly, the measurement of the posterior hippocampus starts when an ovoid mass of gray matter appeared inferiomedially to the trigone of the lateral ventricle. All cornu ammonis segments, dentate gyrus, alveus, parasubiculum, subiculum proper, and prosubiculum were included in the measurement of the posterior hippocampus after the interruption of the pulvinar by the crus of the fornix. The anterior and posterior hippocampi are separated by the appearance of the cistern pontis. The anterior hippocampus measurement began on the first slice where the cistern pontis was visible. The amygdala measurement began when it first appeared posteriorly. We separated the anterior portion of the hippocampus and the amygdala by following the alveus when visible. If this was not readily seen, a straight line was drawn from the most superiomedial portion of the temporal horn laterally to the most medial part of the ambient gyrus (10). Measurement of amygdala, hippocampus, and intracranial volume was made by well-trained and reliable raters (.94 and .98, .95 and .99, .99 and .99, respectively, P.C.E. and L.E.K.), blind to any identifying clinical information. Manual measurement of the amygdala and hippocampus was performed using MEDx 3.30 software (Sensor Systems, Germantown, Maryland). One MDD patient was judged to not have amygdala measurements of sufficient quality due to subject motion to be included in the

Table 1. Demographic Characteristics for Patients with Familial MDD and Healthy Comparison Subjects

	Healthy Comparison Subjects	Patients with Familial MDD		
Item	*n* = 35	*n* = 32	*t*	*p* Value
Age (years)	14.51 (2.72)	14.08 (2.88)	.64	.53
Hamilton Anxiety	2.26 (2.65)	14.38 (6.58)	10.04	<.0001
CDRS	12.17 (10.53)	55.34 (8.83)	15.48	<.0001
Illness Duration (months)	—	27.70 (27.68)	—	—
Sex	13 male, 22 female	12 male, 20 female	—	—

Data are given as mean (SD). Unpaired *t* tests.
CDRS, Childhood Depression Rating Scale-Revised; MDD, major depressive disorder.