Reduced Anterior Cingulate Cortex Glutamatergic Concentrations in Childhood Major Depression

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ABSTRACT

Objective: To examine in vivo glutamatergic neurochemical alterations in the anterior cingulate cortex of children with major depressive disorder (MDD). Method: Single-voxel proton magnetic resonance spectroscopic (1H-MRS) examinations of the anterior cingulate cortex were conducted in 13 psychotropic-naïve children and adolescents with MDD and 13 age- and sex-matched healthy children and adolescents. Ten of the 13 MDD patient–control pairs also had a 1H-MRS examination of occipital cortex. Results: Anterior cingulate glutamatergic (Glx) concentrations were significantly lower (19% decrease) in MDD patients versus controls (9.27 ± 0.43 versus 11.47 ± 0.26, respectively, \( p = .000 \)). Reduced anterior cingulate Glx in MDD patients was associated with increased severity of functional impairment. These results remained comparably significant after controlling for age and anterior cingulate volume. Occipital cortex Glx did not differ between MDD patients and controls. Conclusions: These preliminary findings provide new evidence of localized functional neurochemical marker alterations in Glx in anterior cingulate cortex in pediatric MDD. Altered anterior cingulate Glx neurotransmission may be involved in the pathogenesis of MDD. J. Am. Acad. Child Adolesc. Psychiatry, 2004;43(3):341–348. Key Words: depression, glutamate, anterior cingulate, child, proton magnetic resonance spectroscopy.
trations in specific brain regions of interest. Compounds that can be measured with this technique include glutamate and glutamine (Glx). Recent investigation has increasingly focused on the role of Glx in the pathogenesis of mood disorders, including MDD (Schiffer, 2002; Zarate et al., 2003). Abnormalities in plasma and platelet Glx have been reported in medication-free adults with MDD (Altamura et al., 1993, 1995). Temporary reduction in Glx was observed in two patients receiving chemotherapy for breast cancer with secondary depression (Cousins and Harper, 1996). Using 1H-MRS, Auer et al. (2000) reported reduced Glx in the anterior cingulate cortex, but not in parietal white matter, in 19 adults with MDD and 18 age-matched healthy controls. Reductions in anterior cingulate Glx were most prominent in severely depressed patients. No significant differences in the neuronal marker, N-acetyl-aspartate (Birken and Oldendorf, 1989), choline compounds, creatine/phosphocreatine, or myo-inositol were observed in either the anterior cingulate cortex or parietal white matter in MDD patients versus controls (Auer et al., 2000). More recently, Pfleiderer et al. (2003) reported reduced anterior cingulate Glx in severely depressed adults with MDD; levels increased significantly after successful ECT. Taken together, these studies suggest that altered glutamatergic neurotransmission in the anterior cingulate cortex may be involved in the pathogenesis of MDD.

To our knowledge, although MDD commonly emerges during childhood or adolescence, no prior brain imaging study has examined the anterior cingulate cortex in children and adolescents with MDD prior to exposure to psychotropic medications. In this hypothesis-driven preliminary investigation based on prior volumetric and 1H-MRS studies of Glx in adults with MDD, we predicted decreased Glx in the anterior cingulate cortex in psychotropic-naïve children with MDD versus control subjects.

**METHOD**

Subjects

This research investigation was approved by the Wayne State University Human Investigation Committee. All legal guardians provided written informed consent and all children gave written assent before initiating studies and after having understood all issues involved in participation in the study protocol. Thirteen psychotropic drug-naïve, right-hand-dominant child and adolescent outpatients with MDD and 13 healthy comparison subjects matched for age, gender, weight, height, handedness, and parental socioeconomic status were recruited (Table 1). All patients were recruited through referral to the Wayne State University Child Psychiatry Outpatient Clinic, while controls were referred by local pediatricians, school systems, and the community (e.g., church groups). Depressed patients and healthy controls were paid an honorarium for participating in this research investigation. Children, adolescents, and their parents were assessed by well-trained psychologists experienced in comprehensive pediatric assessment. The Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) was administered using DSM-IV criteria (American Psychiatric Association, 1994). A clinical psychiatric interview was also conducted by a board-certified child psychiatrist (D.R.R.). Exclusion criteria for all patients and controls included prior exposure to psychotropic medication, any lifetime history of psychosis, bipolar disorder, obsessive-compulsive disorder, eating disorder, conduct disorder, substance abuse or dependence disorder, Tourette syndrome and other tic-related disorders, autism, mental retardation or learning disabilities, or

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MDD Patients</th>
<th>Comparison Subjects</th>
<th>t(^{a})</th>
<th>p(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>15.54 ± 2.39</td>
<td>15.36 ± 2.48</td>
<td>0.19</td>
<td>.85</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>13</td>
<td>13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Male (n)</td>
<td>5</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female (n)</td>
<td>8</td>
<td>8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>height (inches)</td>
<td>64.75 ± 5.14</td>
<td>64.54 ± 6.62</td>
<td>0.28</td>
<td>.78</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>130.00 ± 27.31</td>
<td>130.69 ± 40.24</td>
<td>0.051</td>
<td>.96</td>
</tr>
<tr>
<td>Parental SES(^{c})</td>
<td>2.77 ± 1.17</td>
<td>2.69 ± .95</td>
<td>0.19</td>
<td>.86</td>
</tr>
<tr>
<td>Age at onset of 1st clinical presentation (yr)</td>
<td>12.17 ± 1.12</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (yr)</td>
<td>3.16 ± 3.65</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Note:* Patients were psychotropic medication-naïve. Data are presented as mean ± SD unless otherwise indicated. MDD = major depressive disorder.

\(^{a}\) Independent t statistic.

\(^{b}\) Two-tailed significance.

\(^{c}\) Parental SES measures parental socioeconomic status based on parental education and occupational functioning (Hollingshead, 1975) from 1 (highest) to 5 (lowest).
significant medical or neurologic disorders. Eight of the 13 patients with MDD had a comorbid psychiatric disorder(s), including 4 with comorbid anxiety disorders, 1 with comorbid attention-deficit disorder without hyperactivity, 1 with comorbid oppositional defiant disorder (ODD), and 2 with comorbid anxiety disorders and ODD. Five patients had MDD as their sole diagnosis. Healthy comparison subjects had no history of psychiatric illness and no DSM-IV Axis I disorder in any of their first-degree relatives. Detailed medical and neurological histories were obtained from all children and their parents. All children had a physical examination within the past year by their pediatrician/family physician and were considered physically healthy.

Clinical Measures

Functional impairment in MDD patients was measured with the Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976) (mean score 5.08, SD = 0.76). This score is anchored so that scores of 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill. The Childhood Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985), measured severity of depressive symptoms (mean score 59.08, SD = 8.80). All patients with MDD had a CDRS-R score of at least 43, indicating significant dysfunction. The Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), measured severity of anxiety (mean score 15.15, SD = 4.36).

MRI Protocol

Integrated volumetric MRI and 1H-MRS studies were performed in the same scanning session on the same day at the Children’s Hospital of Michigan Imaging Center using a Signa Horizon 1.5-Tesla unit (GE Medical Systems, Milwaukee, WI). Scanning was completed in approximately 60 minutes and all children were given earplugs to help reduce noise disturbances. Comfortable head positioning and stability in the quadrature radiofrequency head coil was achieved with foam cushioning and Velcro straps. Children were monitored at all times by audio link and peripheral pulse oximetry monitoring. The volumetric image acquisition and analysis components of this study have been published elsewhere (Gilbert et al., 2000; Keshavan et al., 1997; MacMillan et al., 2003; Nolan et al., 2002; Rosenberg et al., 1997; and are, therefore, not described here.

For each subject, 1H-MRS spectra were acquired on the 1.5-Tesla MRI scanner using a short-echo single voxel double spin-echo point-resolved spectroscopy (PRESS) pulse sequence (Bottomley, 1987) from a $2 \times 1.5 \times 1 \text{ cm} = 3 \text{ cc}$ voxel centered in the anterior cingulate cortex (Fig. 1). 1H-MRS acquisition and analysis procedures are described in detail in our prior reports (Benazon et al., 2003; De Bellis et al., 2001; De Bellis et al., 2000; De Bellis et al., 1999; De Bellis et al., 1998) and are only briefly described here. Compared to the stimulated echo acquisition mode (STEAM) pulse sequence of equal echo time (TE) and repetition time (TR) (Frahm et al., 1990), the PRESS pulse sequence provides double the signal-noise ratio per unit time. Acquisition parameters were $\text{TE} = 30 \text{ msec}, \text{TR} = 3 \text{ sec}$ with 512 averages. The short echo time of 30 msec minimized T2 signal decay and the repetition time of 2,000 msec minimized T1 error resulting from collecting spectra under less than fully relaxed conditions. After the scanning procedure was completed, the raw time domain spectral files were stored automatically and downloaded via FTP on a UNIX workstation networked to the MR scanner computer. A hard copy of the MR image with precise voxel coordinates and Fourier-transformed spectrum was obtained from the scanner console for archiving. Scans with motion artifact ($n = 1$) were excluded. Five patients diagnosed with MDD subsequently refused to have an MRI scan.

Neurochemical compounds that can be identified by short-echo 1H-MRS at 1.5 Tesla include Glx, the neuronal marker N-acetylaspartate (NAA) (Birken and Oldendorf, 1989), choline compounds (Cho), creatine/phosphocreatine (Cr), and myo-inositol (mI). All 1H-MRS data were analyzed with the established LCModel method (licensed by S.W. Provencher, Max-Planck-Institute, Gottingen, Germany), which has a user community representing over 100 MR research groups in the United States and Europe. This user-independent fitting technique is straightforward and reliable, as validated by several groups, including our own laboratory (Benazon et al., 2003; Bolton et al., 2001; De Bellis et al., 2000; Frahm and Hanefeld, 1996; Provencher, 2001). Spectral signal assignments for Glx, NAA, Cho, Cr, and mI were performed by using estimations from an external standard representing the spectra of phantoms containing known concentrations of these compounds. LCModel enables quantification of metabolites with overlapping signals by employing a library of concentration-calibrated model spectra of all compounds as an a priori database. This enables assignment of MRS signals to their appropriate frequencies. Because of its highly automated features, the subjectivity involved in measuring spectral peak areas with older methods was eliminated (Provencher, 2001).

A 1H-MRS voxel (8 cc) was also placed in the occipital gray matter (Fig. 2) in 10 of the 13 MDD patient–control pairs to address local anterior cingulate versus more global brain effects. The occipital lobe region of interest is a well-characterized region in normal adult and child studies (Barker et al., 1993; Kreis et al., 1993) and is a gray matter region less implicated in the neuro-pathophysiology of MDD. Its high magnetic field homogeneity facilitates acquisition of high-quality spectra.

An experienced, trained technician blind to clinical data placed the anterior cingulate and occipital voxels at the same slice level for all MDD patients and controls using a systematic, validated approach for voxel placement (Moore et al., 1999, 2000).

Data Analysis

Anterior cingulate and occipital metabolite concentrations were analyzed using independent $t$ tests to assess for differences between MDD patients and controls. Because of prior investigations demonstrating volumetric abnormalities in the prefrontal cortex and in regions of the anterior cingulate cortex in adults with MDD (Botton et al., 2002; Drevets et al., 1992, 1997) and in a similar sample of children and adolescents with MDD (Nolan et al., 2002) and because of possible effects of age on MRI measures, analyses of covariance controlling for age and anterior cingulate volume were also used to assess for case–control differences in metabolite concentrations. Correlations of Glx and NAA and clinical inventories representing over 100 MR research groups in the United States and Europe, which has a user community

RESULTS

A significant decrease (19%) in Glx was observed in the anterior cingulate cortex ($t_{24} = 4.01, p = .000; F_{1,22} = 16.50, p = .001$) but not in the occipital cortex ($t_{18} = 0.97, p = .344; F_{1,17} = 0.99, p = .333$) in MDD patients versus controls (Fig. 3, Table 2). Reduced anterior cingulate Glx in MDD patients was inversely correlated with increased functional impairment as
measured by the CGI-S ($r = -0.66, p = .021$) but was not correlated with depressive symptom score as measured by the CDRS-R or with illness duration. Anterior cingulate Cr ($t_{24} = 2.34, p = .028; F_{1,22} = 5.01, p = .036$) but not occipital Cr concentrations ($t_{18} = 0.12, p = .906$) were also significantly decreased in MDD patients versus controls. Cr concentrations were not correlated with functional impairment, depressive symptom severity, or illness duration. No significant differences between MDD patients and controls were observed in anterior cingulate NAA ($t_{24} = 1.36, p = .188; F_{1,22} = 2.05, p = .166$), Cho ($t_{24} = 1.74, p = .10; F_{1,22} = 1.90, p = .18$), or ml ($t_{24} = 1.64, p = .11; F_{1,22} = 2.34, p = .14$) nor in occipital NAA ($t_{18} = 0.274, p = .787; F_{1,17} = 0.11, p = .749$), Cho ($t_{18} = 0.02, p = .988; F_{1,17} = 0.002, p = .963$), or ml ($t_{18} = 0.11, p = .917; F_{1,17} = 0.01, p = .913$).

DISCUSSION

Clinical Implications

To our knowledge, this is the first neuroimaging study of children with MDD demonstrating localized decreased anterior cingulate Glx concentrations. These findings replicate and extend the findings of Auer et al. (2000) and Pfleiderer et al. (2003) in studies that demonstrated reduced anterior cingulate Glx concentrations in severely depressed unipolar adults. Our study provides important new data about disturbances in anterior cingulate Glx neurotransmission without the po-
potential confounds of CNS-active medications and with less potential influence of illness progression. Specifically, abnormalities in anterior cingulate Glx may be associated with the clinical presentation of MDD, and this pathological involvement may be an early and central neurobiological deficit in this illness. Moreover, increased glutamate and glutamine levels have been observed in the frontal lobe in medication-free children with bipolar disorder and attention-deficit/hyperactivity disorder (Castillo et al., 2000; MacMaster et al., 2003). Increased anterior cingulate glutamate has also been reported in adults with schizophrenia (Theberge et al., 2002). Thus, reduced anterior cingulate Glx concentrations may differentiate patients with MDD from patients with bipolar disorder, schizophrenia, and ADHD, although further study and direct comparisons across diagnostic groups are necessary.

Normal metabolism of glutamate is critically dependent upon intact neuronal and glial cell density and function (Gallo and Ghiani, 2000; Magistretti et al., 1999). Postmortem investigation of patients with MDD has demonstrated alterations in neuronal and glial cell density in the anterior cingulate cortex (Ongur et al., 1998; Rajkowska, 2000). In vivo structural and functional neuroimaging studies in patients with MDD have also identified reduction in volume and perfusion in the anterior cingulate cortex (Bench et al., 1995; Botteron et al., 2002; Drevets et al., 1992, 1997; Ebert and Ebmeier, 1996; Goodwin, 1996). Preclinical neuroimaging studies suggest that glutamatergic neural activity parallels brain glucose metabolism (Sibson et al., 1997). Therefore, decreased anterior cingulate Glx concentrations in MDD patients may be consistent with prior reports of reduced volume, perfusion, and metabolism in this region.

Prior investigation has demonstrated distinct structural, neurochemical, and functional alterations in prefrontal cortical regions, including the anterior cingulate cortex, between adults and children with familial MDD (patients with at least one first-degree relative...
with MDD) and nonfamilial patients with MDD (patients with no obvious family history of MDD) (Botteron et al., 2002; Drevets et al., 1992, 1997; Farchione et al., 2002; Nolan et al., 2002; Ongur et al., 1998). The sample size in the present study, which included seven patients with familial MDD and six patients with nonfamilial MDD, precluded comprehensive analysis to adequately discriminate distinct alterations in anterior cingulate Glx in familial versus nonfamilial MDD. However, in our sample, significant intergroup differences among patients with familial MDD, nonfamilial MDD, and controls were observed ($F_{2,21} = 15.56, p = .0001$). Anterior cingulate Glx concentrations were decreased in nonfamilial patients with MDD compared to both controls (8.28 mmol/L ± 0.57 versus 11.48 mmol/L ± 0.26, $p = .026$) and patients with familial MDD (8.28 mmol/L ± 0.57 versus 10.14 mmol/L ± 0.42, $p = .021$). Patients with familial MDD also tended to have lower anterior cingulate Glx concentrations than controls (10.14 mmol/L ± 0.42 versus 11.48 mmol/L ± 0.26, $p = .052$).

The meaning of reduced anterior cingulate concentrations of Cr in the MDD patients is unclear. The Cr peak includes both creatine and phosphocreatine with very high concentrations of the high-energy phosphate, phosphocreatine, in the brain. Thus, reduced anterior cingulate Cr concentrations in psychotropic-naive patients with MDD may reflect decreased energy utilization in the anterior cingulate cortex. $^{31}$Phosphorous spectroscopy may help to better delineate the role of Cr in the pathogenesis of MDD by discriminating the individual constituents of the Cr resonance.

Limitations

Although our findings are consistent with prior investigation in adults with MDD (Auer et al., 2000; Pfleiderer et al., 2003) and with the recently proposed glutamatergic deficiency model for MDD (Pfleiderer et al., 2003), they must be considered preliminary because of the several limitations of the study. The anterior cingulate cortex plays a key role in processing both emotional and attentional information (Elliott et al., 2002). Discriminating anterior cingulate dysfunction secondary to attentional versus emotional impairment is necessary, particularly since both may be involved. Our use of semistructured interviews, such as the K-SADS, coupled with clinical psychiatric assessment may not have adequately identified the presence of predominantly inattentive subtypes of attention-deficit/hyperactivity disorder. Future study using more sensitive screening strategies (e.g., continuous performance tasks performed in conjunction with MRS studies) is clearly warranted.

One major potential confound is that the Glx region of the $^1$H-MRS spectrum consists of overlapping resonances of glutamate, glutamine, and $\gamma$-aminobutyric acid (GABA). However, there is evidence to suggest that the Glx region from the anterior cingulate cortex is predominantly glutamate (Auer et al., 2000; Pouwels and Frahm, 1998). For example, glutamine may be primarily localized to cerebral astrocytes (Ross, 1991), and GABA levels in the brain are considerably lower than glutamate and glutamine levels (approximately 1 mmol/kg brain tissue versus approximately 12–14 mmol/kg brain tissue, respectively) (Sanacora et al., 1999). We took the conservative approach, measuring the Glx complex as a grouped value, and did not attempt to separate out the various components of the Glx complex at 1.5 Tesla. There is a growing consensus that the individual components of the Glx region are more reliably measured with spectral editing techniques at higher magnetic field strength (Bartha et al., 2000, 2005).

### TABLE 2

<table>
<thead>
<tr>
<th>Resonance (mM)</th>
<th>Anterior Cingulate Cortex ($n = 13$)</th>
<th>Occipital Cortex ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment-Naïve MDD</td>
<td>Healthy Controls</td>
</tr>
<tr>
<td>Glx</td>
<td>$9.28 ± 1.53$</td>
<td>$11.48 ± 0.94$</td>
</tr>
<tr>
<td>NAA</td>
<td>$6.66 ± 0.98$</td>
<td>$7.50 ± 2.02$</td>
</tr>
<tr>
<td>Cho</td>
<td>$0.84 ± 0.23$</td>
<td>$1.05 ± 0.36$</td>
</tr>
<tr>
<td>Cr</td>
<td>$4.44 ± 0.75$</td>
<td>$5.40 ± 1.27$</td>
</tr>
<tr>
<td>mI</td>
<td>$3.04 ± 0.73$</td>
<td>$3.53 ± 0.82$</td>
</tr>
</tbody>
</table>

*Note: Data given as mean ± SD. mM = millimolar absolute concentration; MDD = major depressive disorder; Glx = glutamate/glutamine; NAA = N-acetyl-aspartate; Cho = choline compounds; Cr = creatine/phosphocreatine; mI = myo-inositol.*
1997; Theberge et al., 2002). Therefore, we acknowledge the potential confound of overlapping resonances. However, the present study of psychotropic-naïve children with MDD replicates the findings of Auer et al. (2000) and Pfeiferer et al. (2003) in adults with MDD and suggests that these observations may potentially be generalizable to the many centers where clinical 1.5-Tesla MRI scanning machines are available.

Our single-voxel study of the anterior cingulate cortex cannot rule out more generalized neurochemical abnormalities in MDD in other brain circuits implicated in MDD (i.e., other prefrontal cortical regions, the amygdala, hippocampus, and striatum). Reduced Glx levels have also been observed in the amygdala, a region with extensive interconnections with the anterior cingulate cortex (LeDoux, 2000), in severely depressed adults with MDD (Michael et al., 2003). Multivoxel MRS studies are necessary to examine additional brain circuits in the same patients with MDD. However, neurochemical abnormalities were not observed in occipital gray matter, nor in parietal white matter (Auer et al., 2000), regions less implicated in the pathogenesis of MDD.

Taken together, these findings suggest decreased localized anterior cingulate Glx in treatment-naïve children with MDD associated with the clinical presentation of MDD. Reduced anterior cingulate Glx may, therefore, represent an early neurobiological marker of MDD. Alternatively, reduced anterior cingulate Glx in patients with MDD may be an epiphenomenon of the underlying psychopathology of illness. However, given the familial nature of MDD, particularly pediatric MDD, coupled with the fact that acquired lesions of the anterior cingulate cortex produce increased emotionality and sensitivity to sad events (Hornak et al., 2003), it is possible that behavioral, anatomical, and biochemical features of MDD reflect a common underlying genetic effect (Drevets et al., 1992, 1997; Ongur et al., 1998). Future MRS studies in other brain regions in pediatric MDD, such as additional subdivisions of the prefrontal cortex, striatum, and temporolimbic cortex, are necessary to determine whether alterations in Glx are localized to the anterior cingulate cortex or are also observed in other brain regions. Because MRS is noninvasive, without ionizing radiation risks, it lends itself well to longitudinal study of brain Glx in patients with MDD before and after treatment intervention over the course of illness. Given evidence that the tricyclic antidepressant desipramine stimulates glutamate release in vitro (Bouron and Chatton, 1999) and that alterations in Glx may be reversible in patients with MDD (Cotter et al., 2001; Michael et al., 2003; Pfeiferer et al., 2003) and in childhood-onset neuropsychiatric disorders (e.g., obsessive-compulsive disorder; Rosenberg et al., 2000), longitudinal study of Glx in MDD could facilitate the identification of critical neurodevelopmental aberrations that might ultimately prove useful for treatment of the illness.

REFERENCES


Bartha R, Williamson PC, Drost DJ et al. (1997), Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry 54*:959–965


Bouron A, Chatton JY (1999), Acute application of the tricyclic antidepressant desipramine presynaptically stimulates the exocytosis of glutamate in the hippocampus. *Neuroscience 90*:729–736


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


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

Frahm J, Hanefeld F (1996), Localized proton magnetic resonance spectroscopy of cerebral metabolites. *Neuropsychopharmacology* 27:64–69


Gilbert AR, Moore GJ, Keshavan MS et al. (2000), Decrease in thalamic volumes of pediatric obsessive compulsive disorder patients taking paroxetine. *Arch Gen Psychiatry* 57:449–456


Horrnak J, Bramham J, Rolls ET et al. (2003), Changes in emotion after circumcised surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 126:1691–1712

Hollingshead AB (1975), *Four Factor Index of Social Status*. New Haven, CT: Yale University Department of Sociology


Mayberg HS, Brannan SK, Mahurin RK et al. (1997), Cingulate function in depression: a potential predictor of treatment response. *NeuroReport* 8:1057–1061


Nolan CL, Moore GJ, Madden R et al. (2002), Prefrontal cortical volume in childhood-onset major depression: preliminary findings. *Arch Gen Psychiatry* 59:173–179


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


Provencher SW (2001), Automatic quantitation of localized in vivo 1H spectra with LCM. *NMR Biomed* 14:260–264


Rosenberg DR, Keshavan MS, O’Hearn KM et al. (1997), Fronto-striatal measurement of treatment-naive pediatric obsessive compulsive disorder. *Arch Gen Psychiatry* 54:824–830


Sanacora G, Mason GF, Rothman DL et al. (1999), Reduced cortical y-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 56:1045–1047


