Evidence for Increased Glutamatergic Cortical Facilitation in Children and Adolescents With Major Depressive Disorder

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Context: Converging lines of evidence implicate the glutamate and γ-aminobutyric acid neurotransmitter systems in the pathophysiology of major depressive disorder. Transcranial magnetic stimulation cortical excitability and inhibition paradigms have been used to assess cortical glutamatergic and γ-aminobutyric acid–mediated tone in adults with major depressive disorder, but not in children and adolescents.

Objective: To compare measures of cortical excitability and inhibition with 4 different paradigms in a group of children and adolescents with major depressive disorder vs healthy controls.

Design: Cross-sectional study examining medication-free children and adolescents (aged 9-17 years) with major depressive disorder compared with healthy controls. Cortical excitability was assessed with motor threshold and intracortical facilitation measures. Cortical inhibition was measured with cortical silent period and intracortical inhibition paradigms.

Setting: University-based child and adolescent psychiatry clinic and neurostimulation laboratory.

Patients: Twenty-four participants with major depressive disorder and 22 healthy controls matched for age and sex. Patients with major depressive disorder were medication naive and had moderate to severe symptoms based on an evaluation with a child and adolescent psychiatrist and scores on the Children’s Depression Rating Scale Revised.

Main Outcome Measures: Motor threshold, intracortical facilitation, cortical silent period, and intracortical inhibition.

Results: Compared with healthy controls, depressed patients had significantly increased intracortical facilitation at interstimulus intervals of 10 and 15 milliseconds bilaterally. There were no significant group differences in cortical inhibition measures.

Conclusions: These findings suggest that major depressive disorder in children and adolescents is associated with increased intracortical facilitation and excessive glutamatergic activity.
(GABA ionotropic receptor family A [GABA_A] and GABA metabotropic receptor family B [GABA_B]) neurotransmission plays a critical role in the pathophysiology of MDD in adults, but there is little similar information about child and adolescent depression.

Transcranial magnetic stimulation (TMS) is a promising method for examining glutamate and GABA functioning in children and adolescents. Single- and paired-pulse TMS techniques involve the application of brief magnetic stimulations to the motor cortex while monitoring an electromyographic reading of motor evoked potential (MEP) in a hand muscle such as the abductor pollicis brevis (APB). These measures have good reliability and prior validation.

In this cross-sectional study, a clinical assessment preceded TMS cortical excitability and inhibition measures during a single session. These TMS measures were collected bilaterally and included MT, ICF, CSP, and ICI.

STUDY PARTICIPANTS

The sample consisted of 24 medication-naive child or adolescent patients with MDD and 22 healthy controls matched for age and sex. Depressed patients and healthy controls were not taking antidepressants or any other psychotropic medications prior to enrollment or during this study. Subjects were not receiving any type of psychotherapy during the study. Depressed patients were recruited through the Child and Adolescent Psychiatry Clinic of the Children’s Medical Center, Dallas, Texas. Healthy controls were recruited through advertisements in the Dallas area. This study was approved by the institutional review board of the University of Texas Southwestern Medical Center, Dallas. Prior to clinical evaluation or any study activities, the purpose of the investigation and the study procedures was explained to participants and their parents. Participants provided written assent and their parents provided written informed consent. All participants were assessed by a board-certified child and adolescent psychiatrist (P.E.C.). Assessment included a physical examination, a neurologic examination, and a urine pregnancy test for female participants who had reached menarche. Clinical assessments included the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime (K-SADS-PL) semistructured psychiatric interview, the Children’s Depression Rating Scale–Revised (CDRS-R), and the Quick Inventory of Depressive Symptomatology, Adolescent Version, Self-report.

INCLUSION AND EXCLUSION CRITERIA

Eligible participants were aged 7 to 18 years, male or female, with no risk factors for seizures (history of unprovoked seizures, seizure disorder, history of febrile seizures, family history of epilepsy, prior neurosurgery, or brain tumor), no unstable medical conditions, and no implanted metal. These criteria were confirmed with the TMS Adult Safety Screen and a clinical interview to ensure the safety of participants during the study. Handedness in all participants was confirmed with Oldfield’s Edinburgh Handedness Inventory.

For participants with MDD, the diagnosis was confirmed with a K-SADS-PL semistructured psychiatric interview conducted by a board-certified child and adolescent psychiatrist (P.E.C.) and a PsyD-level child and adolescent psychologist (B.D.K.). Further inclusion criteria included a score of 40 or higher on the CDRS-R. The K-SADS-PL and CDRS-R were used in the interview with each subject and with the subject’s caregiver. Exclusion criteria included comorbid posttraumatic stress disorder, obsessive-compulsive disorder, pervasive developmental disorders, mental retardation, bipolar disorder, schizophrenia, tic disorder, conduct disorder, eating disorders, and substance use disorders.

Healthy controls had to be in excellent health and not meet the criteria for any current or lifetime DSM-IV-TR diagnoses based on the K-SADS-PL semistructured psychiatric interview. Other exclusion criteria for healthy controls were any psychiatric treatment or psychotropic medications ever and family psychiatric history in a first- or second-degree relative.
TMS TESTING

Testing with TMS was conducted as previously described in reports of adult studies. Subjects were seated in a comfortable chair and wore a swim cap during the procedure. All subjects and research team members wore earplugs during testing sessions. Electromyographic readings were recorded from the APB. Muscle relaxation during the procedure was monitored with audio feedback. The TMS was applied to the hand area of the contralateral cortex with a figure-of-8 magnetic coil (diameter, 70 mm per loop) using the Magstim 200 magnetic stimulator device (Magstim Co Ltd). For a determination of resting MT, the TMS coil was held tangentially on the head with the handle backward at 45° laterally from midline. The optimal coil position for stimulation was identified as the location producing the largest MEP with moderately suprathreshold intensities in a resting APB. The optimal coil position was located by moving the coil in 1-cm increments over the presumed motor cortex area. The optimal stimulation site was marked with a black marker to ensure continuity throughout the experiment. The resting MT was defined as the stimulation intensity eliciting an MEP greater than 50 μV in 5 of 10 trials with a relaxed APB. For ICI and ICF (Figure 1) measurements, a subthreshold conditioning stimulus set to 80% of resting MT preceded a suprathreshold test stimulus, which was calibrated to produce an average MEP of 0.5–1.5-mV peak-to-peak amplitude in the contralateral APB. Conditioning stimuli were delivered to the motor cortex prior to the test stimulus in 1 of 5 random interstimulus intervals: 2 milliseconds (ICI-2) and 4 milliseconds (ICI-4) for ICI measures; 10 milliseconds (ICF-10), 15 milliseconds (ICF-15), and 20 milliseconds (ICF-20) for ICF measures. The sequence of administration was counterbalanced to prevent order effects. For ICF and ICI, the change in test stimulus MEP amplitude of each interstimulus interval was expressed as a percentage of the mean unconditioned MEP amplitude. The CSP was measured with a tonically active APB (a 20% maximum contraction), with simultaneous stimulation at 140% of resting MT delivered to the contralateral motor cortex. Ten trials were performed and averaged. The entire process was executed bilaterally to collect cortical excitability and inhibition measures from each hemisphere.

DEPENDENT AND INDEPENDENT VARIABLES AND COVARIATES

The primary outcome measures were MT, ICF, CSP, and ICI. The primary independent variable was patients with MDD vs healthy controls (a binary, categorical, independent variable, with healthy controls as the reference group). The total score on the CDRS-R, sex, and age in years were included as covariates in the models to bolster precision in the evaluation of the relationship between MDD and healthy controls on each outcome measure.

STATISTICAL ANALYSIS

Demographic and clinical characteristics of the 2 groups were reported using mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. To identify any differences between the characteristics of the 2 groups, we used the 2-independent sample t test with the Satterthwaite method for unequal variances for continuous variables and the χ2 test or Fisher exact test for categorical variables.

The primary data analysis was a 2-group (MDD and healthy control) by 2-region (left hemisphere and right hemisphere) linear mixed model analysis of repeated measures. A separate mixed model analysis was conducted for each primary outcome. Restricted maximum likelihood estimation and type 3 tests of fixed effects were used, with the Kenward-Roger correction applied to the variance components covariance structure. The model contained fixed-effects terms for group, region, and group × region interaction. Intercept was included as a random effect. Simple group effects in each region were assessed, as were simple region effects within each group. The total score on the CDRS-R, age, and sex were included as covariates in the model. We performed all statistical analyses using SAS version 9.2 statistical software (SAS Institute, Inc). The mixed model procedures of PROC MIXED in SAS were used for the mixed model analysis. The level of significance for all tests was set at α = .05 (2-tailed). For multiple testing on the tests of main effects, interaction effects, and post hoc tests of simple effects, P values were adjusted using the false discovery rate.

SUBJECTS

The sample consisted of 24 medication-naive children and adolescents with MDD (aged 9–17 years; mean [SD]
age, 13.87 [2.11] years; 14 female) and 22 healthy controls (aged 9-17 years; mean [SD] age, 13.77 [2.18] years; 11 female). Of the 46 adolescents in this study, 13 (28%) had a family history of mood disorder. Family history of mood disorder occurred in 13 of the 24 depressed adolescents (54%) and in none of the 22 healthy controls. The characteristics of the study participants are summarized in Table 1.

### CORTICAL EXCITABILITY

#### Motor Threshold

The MT least squares mean (SE) values were similar for the MDD and healthy control groups (60.90 [5.89] and 54.96 [6.28], respectively). The mixed model repeated-measures analysis revealed no significant main effects of group \( (F_{1,43} = 0.26; \text{ raw } P = .61; \text{ adjusted } P = .71) \), region \( (F_{1,43} = 0.79; \text{ raw } P = .38; \text{ adjusted } P = .58) \), or group \& region interaction \( (F_{1,43} = 0.02; \text{ raw } P = .87; \text{ adjusted } P = .87) \). No significant simple group effects emerged \( (\text{ raw } P > .60; \text{ adjusted } P > .72) \). No significant simple region effects emerged \( (\text{ raw } P > .46; \text{ adjusted } P > .74) \).

### Intracortical Facilitation

#### ICF-10

For ICF-10 values, the mixed model repeated-measures analysis revealed no significant group \& region interaction effect \( (F_{1,43} = 0.54; \text{ raw } P = .47; \text{ adjusted } P = .87) \) and no significant region main effect \( (F_{1,43} = 0.96; \text{ raw } P = .33; \text{ adjusted } P = .58) \), but it did reveal a significant group main effect \( (F_{1,43} = 6.51; \text{ raw } P = .01; \text{ adjusted } P = .03) \). The pattern of the overall adjusted least squares mean (SE) revealed that ICF-10 values were significantly higher for the MDD group than for the healthy control group (1.89 [0.24] vs 0.86 [0.26], respectively; \( \text{ raw } P = .01; \text{ adjusted } P = .03 \) (Table 2). Furthermore, this pattern was found with simple group effects in the left hemisphere \( (\text{ raw } P = .01; \text{ adjusted } P = .04) \) but not in the right hemisphere \( (\text{ raw } P = .03; \text{ adjusted } P = .11) \). No significant simple region effects emerged for adjusted ICF-10 values \( (\text{ raw } P > .22; \text{ adjusted } P > .74) \). The adjusted least squares means for ICF-10 are reported in Table 2.

#### ICF-15

For ICF-15 values, the mixed model repeated-measures analysis revealed no significant group \& region interaction effect \( (F_{1,43} = 0.16; \text{ raw } P = .69; \text{ adjusted } P = .87) \) and no significant region main effect \( (F_{1,43} = 1.17; \text{ raw } P = .29; \text{ adjusted } P = .58) \), but it did reveal a significant group main effect \( (F_{1,43} = 12.77; \text{ raw } P = .001; \text{ adjusted } P = .007) \). The pattern of the overall adjusted least squares mean (SE) revealed that ICF-15 values were significantly higher for the MDD group than for the normal controls (2.49 [0.26] vs 0.61 [0.28], respectively; \( \text{ raw } P = .001; \text{ adjusted } P = .007 \)). Furthermore, simple group effects were significant within both the right hemisphere \( (\text{ raw } P < .001; \text{ adjusted } P < .005) \) and the left hemisphere \( (\text{ raw } P = .001; \text{ adjusted } P = .007) \). No significant simple region effects emerged for adjusted ICF-15 values \( (\text{ raw } P > .31; \text{ adjusted } P > .74) \).

#### Table 1. Characteristics of 24 Children and Adolescents With Major Depressive Disorder Compared With 22 Healthy Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With MDD (n = 24)</th>
<th>Healthy Controls (n = 22)</th>
<th>P Value (FDR-Adjusted P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>13.87 (2.11)</td>
<td>13.77 (2.18)</td>
<td>.87 (.99)</td>
</tr>
<tr>
<td>Sex</td>
<td>9-17</td>
<td>9-17</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (42)</td>
<td>11 (50)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (58)</td>
<td>11 (50)</td>
<td>.57 (.89)</td>
</tr>
<tr>
<td>Left-handed</td>
<td>2 (8)</td>
<td>2 (9)</td>
<td>.99 (.99)</td>
</tr>
<tr>
<td>Family history of mood disorder</td>
<td>13 (54)</td>
<td>0 (0)</td>
<td>&lt;.001 (.002)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>8 (33)</td>
<td>0 (0)</td>
<td>.009 (.02)</td>
</tr>
<tr>
<td>ADHD</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td>.14 (.26)</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>.97 (.99)</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>.97 (.99)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White 15 (62)</td>
<td>8 (36)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2 (8)</td>
<td>11 (50)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (12)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (17)</td>
<td>2 (9)</td>
<td></td>
</tr>
<tr>
<td>Episode duration, mo</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.9 (9.7)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-48</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CDRS-R score</td>
<td>58.9 (8.5)</td>
<td>19.6 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>44-77</td>
<td>17-24</td>
<td></td>
</tr>
<tr>
<td>QIDS-A-R/SR score</td>
<td>12.5 (5.6)</td>
<td>3.4 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4-25</td>
<td>0-7</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2. Intracortical Facilitation Results in 24 Children and Adolescents With Major Depressive Disorder Compared With 22 Healthy Controls

<table>
<thead>
<tr>
<th>TMS Measure</th>
<th>Patients With MDD (n = 24)</th>
<th>Healthy Controls (n = 22)</th>
<th>P Value (FDR-Adjusted P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF-10</td>
<td>2.09 (0.24)</td>
<td>0.86 (0.26)</td>
<td>.01 (.03)</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>1.99 (0.26)</td>
<td>0.84 (0.28)</td>
<td>.03 (.11)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>2.19 (0.25)</td>
<td>0.87 (0.27)</td>
<td>.01 (.04)</td>
</tr>
<tr>
<td>ICF-15</td>
<td>2.49 (0.26)</td>
<td>0.61 (0.28)</td>
<td>.001 (.007)</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>2.46 (0.28)</td>
<td>0.53 (0.30)</td>
<td>&lt;.001 (.005)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>2.53 (0.27)</td>
<td>0.69 (0.29)</td>
<td>.001 (.007)</td>
</tr>
<tr>
<td>ICF-20</td>
<td>1.59 (0.32)</td>
<td>1.12 (0.35)</td>
<td>.47 (.71)</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>1.51 (0.34)</td>
<td>1.12 (0.37)</td>
<td>.55 (.72)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>1.68 (0.33)</td>
<td>1.13 (0.36)</td>
<td>.41 (.72)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CDRS-R, Children’s Depression Rating Scale–Revised; FDR, false discovery rate; MDD, major depressive disorder; NA, not applicable; QIDS-A-R/SR, Quick Inventory of Depressive Symptomatology, Adolescent Version, Self-report.

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adjusted least squares means for ICF-15 are reported in Table 2.

ICF-20. For ICF-20 values, the mixed model repeated-measures analysis revealed no significant group × region interaction effect ($F_{1,37.3} = 0.29$; raw $P = .59$; adjusted $P = .87$), no significant region main effect ($F_{1,37.3} = 0.38$; raw $P = .54$; adjusted $P = .63$), and no significant group main effect ($F_{1,34.9} = 0.54$; raw $P = .47$; adjusted $P = .71$). No significant single group effects emerged for adjusted ICF-20 values (raw $P > .41$; adjusted $P > .72$). No significant simple region effects emerged for adjusted ICF-20 values (raw $P > .41$; adjusted $P > .74$). The adjusted least squares means for ICF-20 are reported in Table 2.

**CORTICAL INHIBITION**

**Cortical Silent Period**

The CSP least squares mean (SE) values were similar for the MDD and healthy control groups (169.2 [17.31] and 176.6 [16.98] milliseconds, respectively). In the MDD group, the CSP least squares mean (SE) of the right hemisphere was 178.6 (17.82) milliseconds, whereas it was 159.8 (17.73) milliseconds for the left hemisphere. The mixed model repeated-measures analysis revealed no significant group × region interaction effect ($F_{1,41.1} = 2.56$; raw $P = .13$; adjusted $P = .52$) and no significant group main effect ($F_{1,36.4} = 0.05$; raw $P = .82$; adjusted $P = .82$), but it did reveal a trend toward a significant region main effect ($F_{1,33.3} = 3.33$; raw $P = .07$; adjusted $P = .49$). Simple region effects revealed a trend toward a significant region difference (left hemisphere vs right hemisphere) on the adjusted CSP values within the MDD group (raw $P = .02$; adjusted $P = .14$) but not within the control group (raw $P = .84$; adjusted $P = .95$). No significant simple group effects emerged for adjusted CSP values (raw $P > .63$; adjusted $P > .72$).

**Intracortical Inhibition**

ICI-2. The ICI-2 least squares mean (SE) values were similar for the MDD and healthy control groups (0.51 [0.10] and 0.41 [0.11], respectively). The mixed model repeated-measures analysis revealed no significant group × region interaction effect ($F_{1,39.9} = 0.09$; raw $P = .77$; adjusted $P = .87$), no significant region main effect ($F_{1,60.7} = 0.17$; raw $P = .68$; adjusted $P = .68$), and no significant group main effect ($F_{1,37.7} = 0.26$; raw $P = .61$; adjusted $P = .71$). Simple group effects showed that adjusted ICI-2 values were also statistically similar between the 2 groups within each hemisphere. No significant simple region effects emerged for adjusted ICI-2 values (raw $P > .62$; adjusted $P > .93$).

ICI-4. The ICI-4 least squares mean (SE) values were similar for the MDD and healthy control groups (0.68 [0.14] and 0.45 [0.15], respectively). The mixed model repeated-measures analysis revealed no significant group × region interaction effect ($F_{1,41} = 2.13$; raw $P = .15$; adjusted $P = .52$), no significant region main effect ($F_{1,41.2} = 0.66$; raw $P = .42$; adjusted $P = .58$), and no significant group main effect ($F_{1,39.1} = 0.70$; raw $P = .41$; adjusted $P = .71$). No significant simple group effects emerged for adjusted ICI-4 values. No significant simple region effects emerged for adjusted ICI-4 values (raw $P > .12$; adjusted $P = .74$).

**TESTING FOR THREAT TO VALIDITY BY FAMILY HISTORY OF MOOD DISORDER**

To examine whether family history of mood disorder affected the basic interpretation of our findings on cortical excitability and inhibition, we conducted similar linear mixed model repeated-measures analyses with family history of mood disorder (along with age, sex, and CDKS-R total score included as covariates in each model). The basic results and conclusions did not differ from those reported herein (results not reported).

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**COMMENT**

To our knowledge, this is the first study using TMS to evaluate cortical excitability and inhibition in children and adolescents with MDD. Our results suggest that depression in children and adolescents is associated with increased ICF, a direct neurophysiological corollary of excessive glutamatergic neurotransmission. However, contrary to the inhibition deficits previously reported in adults with depression, no deficits in inhibition, which are mediated through GABAergic mechanisms, were found in children and adolescents with MDD.

Excessive ICF, a neurophysiological index of increased cortical glutamatergic activity, is noteworthy because glutamate dysregulation plays a decisive role in depression and mood disorders. Glutamatergic neurons and synapses make up a major portion of relevant limbic and cortical neurocircuitry. Prior animal research suggests that stress and glucocorticoids may collectively upregulate glutamate neurotransmission through increased presynaptic release and reduced clearance.

Our findings suggest that children and adolescents with MDD have excessive cortical excitability mediated by NMDA receptors. Prior magnetic resonance spectroscopy (MRS) work with depressed adult subjects demonstrated reductions of glutamate metabolites (glutamate/glutamine, glutamate, and glutamine) in the anterior cingulate cortex, the left dorsolateral prefrontal cortex, the dorsomedial prefrontal cortex, and ventromedial prefrontal cortex. Initial MRS work with depressed children and adolescents demonstrated decreased glutamate/glutamine and glutamate concentrations in the anterior cingulate cortex. Currently, drawing definitive conclusions about the pathophysiological implications of our findings in the context of prior MRS studies is problematic because of the complexity and nature of glutamatergic neurotransmission and the vast differences in methodologic approaches.

Although our findings may superficially appear to be at odds with previous findings of deficient cortical glutamate in depressed subjects, collectively this difference may simply suggest that there is less free glutamate with...
increased glutamatergic neurotransmission. The ICF paradigm is a direct measure of “active” NMDA neurotransmission rather than of free glutamate in the brain. Therefore, low concentrations of glutamate as identified by MRS may suggest increased glutamate expenditure or turnover from hyperactive, excitatory neurotransmission. Another important consideration is that reduced glutamate measured by MRS may be a consequence of glial abnormalities in MDD. One could postulate that a glial abnormality that reduces the glutamate availability from glial cells might result in compensatory upregulation of NMDA neurotransmission. In vivo studies of glutamate neurotransmission throughout development are crucial in advancing knowledge in this area. Ideal future efforts would involve complementary studies with MRS and TMS or interleaved experiments.

It is intriguing that our CSP and ICI findings did not vary significantly among the depressed participants and the healthy controls. Previously, CSP and ICI deficits in adults with MDD have been a consistent finding. The glutamate and GABA systems have a complex relationship across development that serves to regulate both excitatory and inhibitory functions. Prior work suggests that, compared with adults, children and adolescents may have less cortical inhibition (CSP and ICI deficits) and GABAergic inhibitory functioning. Although CSP measures can be produced reliably as early as age 5 years, no systematic studies to our knowledge have examined the developmental course or the impact of age on this marker of GABAB activity. Our results show a trend in depressed children and adolescents toward hemispheric differences in CSP and GABA function, with a decrease in the left hemisphere as compared with the right. Prior work has identified electroencephalographic hemispheric coherence abnormalities in at-risk adults and depressed children and adolescents. As with these findings, hemispheric differences in CSP may reflect a perturbation in physiological regulatory systems that warrants further study as a potential marker of vulnerability or disease burden. As with CSP measures and GABA function, changes in ICI measures of GABA across development are poorly understood. However, 4 decades of preclinical work have shown that excessive glutamate and NMDA activity is neurotoxic in the central nervous system.

Animal models suggest that glutamate-mediated toxic effects may be more profound in children and adolescents because of developmental differences in the excitatory-inhibitory balance. Hence, it might be predicted that excessive glutamatergic functioning in...
depressed children and adolescents (Figure 2) leads to excitotoxic damage to GABAergic interneurons, with resultant GABAergic deficits in adulthood (Figure 3). Future longitudinal studies of these neurotransmitter systems and neurophysiological measures across wide age ranges would be important in future work. Another consideration regarding the current findings is that a more treatment-refractory and homogeneous sample of adolescents might have yielded findings more in line with those of prior studies of CSP and ICI in adults with MDD. Recent work with healthy controls suggests that children in general have less cortical inhibition than adults, thereby presenting a possible floor effect in our sample.62

This study had several limitations that provide a context in which to consider the findings. First, the sample size was small. Second, this initial study included participants with a broad range of ages and with various clinical presentations. In comparison with adult MDD, childhood and adolescent MDD is much more heterogeneous, and this sample may be more diverse than those in prior adult studies.63 Future efforts might involve more restricted age ranges and use improved selection for disease severity or type on the basis of genetic, clinical, or physiological factors. Third, we did not control for menstrual cycle. Cortical excitability measures can vary across the menstrual cycle.64 Fourth, the depressed and healthy control groups differed in ethnicity. This is a potential limitation, but ethnicity has not been demonstrated to affect cortical excitability measures.65 Fifth, this investigation involved measures of cortical excitability and inhibition of the motor cortex. Although the paradigms that were used are affected by relevant afferent pathways, the direct study of other brain structures such as the dorso-lateral prefrontal cortex would be ideal. Future studies of child and adolescent MDD might take into consideration the recent findings of studies that combined TMS paradigms with electroencephalography.66 Finally, we evaluated patients with MDD and healthy controls at just 1 point in time. Longitudinal studies could better examine the impact of neurodevelopment and treatment on cortical excitability and inhibition measures.

In conclusion, to our knowledge, this examination is the first to investigate cortical excitability and inhibition measures in children and adolescents with MDD. Our findings demonstrate that these measures can be used in the investigation of mood disorders during development. They provide evidence that children and adolescents with MDD have increased ICF and cortical glutamatergic activity. Future work might evaluate these paradigms as biomarkers and further elucidate the neurophysiology of psychiatric disorders in children and adolescents. Longitudinal studies with larger, well-defined samples are warranted to better examine the trajectories of these neurotransmitter systems and the impact of treatment. Further complementary and correlational studies of TMS and MRS would also advance understanding of the glutamate system and its role in the pathophysiology of adult and childhood mood disorders.
Submitted for Publication: April 4, 2012; final revision received June 21, 2012; accepted July 4, 2012.
Published Online: January 9, 2013. doi:10.1001/2013.jamapsychiatry.24

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Author Contributions: Dr Croarkin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: Dr Croarkin has received research grant support from Stanley Medical Research Institute, NARSAD (now Brain and Behavior Research Foundation), and Pfizer Inc and has served as a site subinvestigator or principal investigator (without additional compensation) for Eli Lilly and Co, Forest Laboratories Inc, Merck and Co Inc, and Pfizer Inc. Dr Hu is has received research grant support from the National Institutes of Health, NARSAD, Stanley Medical Research Institute, Cyberonics Inc, Neuronetics Inc, Advanced Neuromodulation Systems Inc (now part of St Jude Medical Inc), Brainways Ltd, and NeoSync Inc and has received a grant-in-kind for equipment from Magstim Co Ltd. Dr Emslie has received research and grant support from the National Institutes of Health, BioBehavioral Diagnostics Co, Eli Lilly and Co, Forest Laboratories Inc, GlaxoSmithKline PLC, Shire PLC, and Somerset Pharmaceuticals Inc; has served as a consultant for BioBehavioral Diagnostics Co, Bristol-Myers Squibb Co, Eli Lilly and Co, INC Research LLC, Lundbeck, Pfizer Inc, Seaside Therapeutics Inc, Shire PLC, Valeant Pharmaceuticals International Inc, Validus Pharmaceuticals LLC, and Wyeth Pharmaceuticals Inc (now part of Pfizer Inc); and has served on speakers’ bureaus for McNeil Consumer Healthcare (now part of Ortho-McNeil-Janssen Pharmaceuticals Inc, a subsidiary of Johnson and Johnson Services Inc) and Forest Laboratories Inc. Dr Kozel has received research and salary support from a US Department of Defense grant and prior grant support from the National Institute of Mental Health and the National Center for Research Resources; has received a grant-in-kind from Neuronetics Inc for supplies and the use of equipment; and has received research grants from the Defense Academy for Credibility Assessment (formerly the Department of Defense Polygraph Institute; now the National Center for Credibility Assessment), Cephos Corp, and Stanley Medical Research Institute. Dr Daskalakis has received external funding from Neuronetics Inc, Brainways Ltd, and Aspect Medical Systems Inc; has received travel allowances from Pfizer Inc and Merck and Co Inc; has received speaker honoraria through Septracor Inc (now Sunovion Pharmaceuticals Inc); and has served on the advisory board of F. Hoffmann-La Roche Ltd.

Funding/Support: This work was supported by the Ontario Mental Health Foundation, the Canadian Institutes of Health Research, the Grant Family through the Centre for Addiction and Mental Health Foundation, and NARSAD (now Brain and Behavior Research Foundation).

Role of the Sponsors: The sponsors had no role in the study design and conduct; collection, management, analysis, and interpretation of data; or preparation, review, or approval of the manuscript.

Online-Only Material: Listen to an author interview about this article, and others, at http://bit.ly/L4AZtw.

Additional Contributions: Anosha Zanjani, BSc, assisted in preparing the figures and Joshua M. Baruth, PhD, and Taryn Mayes, MS, provided review and thoughtful feedback.

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