Published in final edited form as:

J Affect Disord. 2016 January 15; 190: 566–575. doi:10.1016/j.jad.2015.10.020.

Cortical Inhibitory and Excitatory Correlates of Depression Severity in Children and Adolescents

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Abstract

Objectives—Neurophysiologic correlates of depression severity potentially have great utility in diagnosis and treatment planning. Transcranial magnetic stimulation (TMS) measures of cortical inhibition and excitability have shown promise as biomarkers in psychiatry, but no prior work has examined correlates of illness severity in pediatric mood disorders. This study sought to examine the relationship between depression severity and TMS measures of cortical inhibition and excitability in children and adolescents.

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Contributors

Dr. Lewis participated in statistical analysis, interpretation of results, and the writing of the manuscript. Dr. Nakonezny participated in statistical analysis and the writing of the manuscript. Drs. Ameis and Vande Voort participated in interpretation of results and editing the manuscript. Drs. Husain, Emslie, and Daskalakis participated in study design and editing the manuscript. Dr. Croarkin participated in study conceptualization and design, statistical analysis, interpretation of results, and the writing of the manuscript. All authors gave approval of the manuscript for publication. Drs. Lewis and Croarkin have full access to the reported dataset and accept responsibility for the integrity of the statistical analysis.

Disclosures

Drs. Nakonezny and Vande Voort have no financial disclosures.

Methods—Twenty-four depressed and 22 healthy control youth underwent TMS testing (cortical silent period [CSP], short-interval intracortical inhibition at 2-ms and 4-ms interstimulus intervals (ISIs) [SICI-2,-4], resting motor threshold [RMT] and intracortical facilitation at 10-, 15-, and 20-ms ISIs [ICF-10,-15,-20]). Symptom severity was assessed with the Quick Inventory of Depressive Symptomatology (QIDS-A₁₇-SR) and the Children's Depression Rating Scale-Revised (CDRS-R).

Results—In the overall sample, the following significant negative correlations were observed: CDRS-R and CSP (right hemisphere, $\rho=-0.35$, $p=0.021$); QIDS-A₁₇-SR and CSP (left, $\rho=-0.33$, $p=0.031$; right, $\rho=-0.42$, $p=0.004$); and CDRS-R and SICI-4 (right, $\rho=-0.30$, $p=0.042$). Among healthy control participants, additional significant negative correlations were observed between QIDS-A₁₇-SR and right ICF-10; QIDS-A₁₇-SR and right ICF-15; and QIDS-A₁₇-SR and left ICF-20. Among depressed participants, significant negative correlations were observed between QIDS-A₁₇-SR and bilateral CSP; CDRS-R and bilateral ICF-10; CDRS-R and bilateral ICF-15; QIDS-A₁₇-SR and left ICF-10; and QIDS-A₁₇-SR and bilateral ICF-15.

Limitations—Small sample, potential developmental/age- and sex-related effects.

Conclusions—These preliminary results provide evidence for a relationship between depression severity and dysfunction in GABAergic and glutamatergic cortical processes in a pediatric population.

Keywords

Cortical inhibition; Intracortical facilitation; GABA; Glutamate; Transcranial magnetic stimulation; Child and adolescent depression

1. Introduction

Depression is a common condition in pediatric populations and is a significant public health concern. Among adolescents in the U.S., the point prevalence of depression has been estimated at 4.3% (Pratt and Brody, 2008), with prevalence of major depression rising as high as 16%–17% over the adult lifespan (Andrade et al., 2003; Kessler et al., 2003). Globally, major depression is a leading cause of disease burden, ranking among the top five internationally (Lopez et al., 2006; Mathers and Loncar, 2006) and projected to increase in the coming decades (Mathers and Loncar, 2006). Depression also is associated with suicide, which is the second leading cause of death among adolescents and young adults in the U.S. (Hoyert and Xu, 2012; Centers for Disease Control and Prevention, 2013). A recent study found that 7.8% of surveyed adolescents reported having made a suicide attempt within the past twelve months (Eaton et al., 2012). In spite of this high prevalence and the significant morbidity and mortality associated with depression in children and adolescents, the pathophysiology of depression in this age group remains poorly understood. Prior research indicates that the neurobiology of depression in children and adolescents may differ from that in adults. Previous studies have shown that hypothalamic-pituitary-adrenal axis hormone activity, growth hormones, and serotonergic receptor responsiveness diverge in pediatric and adult depressive disorders (Zalsman et al., 2006). Additionally, there is substantial evidence that excitatory and inhibitory neurotransmitter systems undergo significant changes in structure and function during development (Duncan et al., 2010;

Chugani et al., 2001; Rakhade and Jensen, 2009), particularly in the context of depression (Croarkin et al., 2014). In clinical practice, however, the assessment of depression severity and risk remains largely uninformed by pathophysiology. There is growing recognition that traditional diagnostic approaches are inadequate, and new initiatives are underway to develop objective biological markers to aid with diagnosis, early identification, treatment selection, and clinical monitoring (Singh and Rose, 2009).

Gamma-aminobutyric acid (GABA) and glutamate are, respectively, the primary inhibitory and excitatory neurotransmitters in the brain. Prior work has examined the putative roles of GABA and glutamate in the pathophysiology of major depression (Croarkin et al., 2011; Krystal et al., 2002; Levinson et al., 2010; Sanacora and Saricicek, 2007). Various methods have been employed to study disruptions in GABAergic inhibitory systems in depressed individuals, including measurements of serum and cerebrospinal fluid GABA levels (Sanacora, 2010). Proton magnetic resonance spectroscopy studies have demonstrated that adults (Hasler et al., 2007; Sanacora et al., 2004; Sanacora et al., 1999) and adolescents (Gabbay et al., 2012) with depression have decrements in cortical GABA compared to healthy comparison groups. Additionally, antidepressant treatments, including the serotonin reuptake inhibitors and electroconvulsive therapy, have been shown to correct GABAergic deficits in depressed individuals (Krystal et al., 2002). Antidepressant effects also have been noted with medications possessing antagonistic properties at the *N*-methyl-D-aspartate (NMDA) glutamate receptor, including the antibiotic D-cycloserine (Crane, 1959; Krystal et al., 1997), the antiviral/antiparkinsonian agent amantadine (Dietrich et al., 2000; Vale et al., 1971), and other experimental compounds (Dutta et al., 2015). Perhaps most notably, the anaesthetic agent ketamine, an NMDA antagonist, also has received much attention in recent years for its rapid antidepressant effect at subanesthetic doses (Zarate et al., 2006; for review, see Dutta et al., 2015), suggesting dysfunction in glutamatergic systems in the pathophysiology of major depression. However, despite the growing evidence in the adult literature for roles of GABAergic and glutamatergic dysregulation in depression, there remains a paucity of work focused on these systems in depressed children and adolescents.

Single- and paired-pulse transcranial magnetic stimulation (TMS) are neurophysiologic techniques that involve the application of a focused magnetic pulse that induces a transient electrical current in the cerebral cortex, allowing examination of the GABAergic and glutamatergic function of neural circuits noninvasively and in vivo. Particular TMS paradigms index specific excitatory and inhibitory neurotransmitter receptor functioning (Radhu et al., 2013) as demonstrated by studies of observed responses to TMS stimulation when pharmacologic agents with known GABAergic and glutamatergic receptor properties are administered (Siebner et al., 1998; Werhahn et al., 1999; Ziemann, 2004; Ziemann et al., 1996a). Other neurophysiologic studies have delineated distinct TMS paradigms for indexing GABAergic and glutamatergic receptor-mediated activity (Sanger et al., 2001).

A recent meta-analysis by Radhu and colleagues (Radhu et al., 2013) found that the existing TMS literature indicates significant reductions in the duration of the cortical silent period (CSP; a TMS paradigm measuring GABA_B-mediated inhibition) and short-interval intracortical inhibition (SICI; a TMS index of GABA_A-mediated inhibition) amplitude in adults with major depression compared to healthy controls. TMS measures of glutamatergic

functioning, such as resting motor threshold (RMT) and intracortical facilitation (ICF), have been studied less frequently, with the meta-analysis of existing studies failing to show significant differences between depressed adults and controls in either RMT or ICF (Radhu et al., 2013). Fewer studies have examined the relationship between cortical inhibitory and excitatory measures and symptom severity; some previous studies have failed to find a significant relationship between cortical inhibition and depression severity (Levinson et al., 2010; Steele et al., 2000), whereas others have noted a significant correlation between CSP, SICI, and ICF and various depression severity measures (Bajbouj et al., 2006; Lefaucheur et al., 2008). Furthermore, TMS methods have not been employed extensively in the study of depression in pediatric populations. Our group previously found that in a medication-naïve sample of children and adolescents, those with major depression had elevated ICF in both hemispheres compared to healthy controls; however, no group differences in TMS measures of cortical inhibition were observed (Croarkin et al., 2013). The present exploratory study examined the relationship between TMS measures of excitatory and inhibitory neurotransmission and depression severity in a pediatric sample. Based on our previous findings in this population, we hypothesized that ICF amplitude would correlate with depressive symptom severity. Although our previous study in this age group did not find differences in CSP or SICI between depressed and control participants, the adult literature consistently has shown deficits in these measures of cortical inhibition in depression, and thus we also hypothesized that CSP and SICI would demonstrate correlations with depression severity measures.

2. Method

2.1 Study Design and Overview

This was a cross-sectional study of depressed youth and healthy controls. All participants had a clinical evaluation and TMS testing. Measures of cortical inhibition (SICI, CSP) and excitability (MT, ICF) were collected during a single session. Study design details have been published previously (Croarkin et al., 2013; Croarkin et al., 2014). All study procedures were approved by the local institutional review board prior to the enrollment. Participants provided written assent, while their parents or legal guardians granted written informed consent. The study protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center at Dallas.

2.2 Participants

The sample consisted of the 24 adolescents with major depressive disorder and 22 healthy control participants that were described in our previous study (Croarkin et al., 2013). Recruitment of depressed adolescents took place in a child and adolescent psychiatry clinic at Children's Medical Center, Dallas, Texas and through local advertising. Healthy control participants were recruited through community advertising. All participants were not taking psychotropic medications (including antidepressants, benzodiazepines, or psychostimulants) and were not participating in psychotherapy at the time of enrollment or during participation in the study.

Eligible participants were male and female adolescents between the ages of 7 and 18 years. Participants in the depressed group met criteria for a major depressive episode at the time enrollment according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (American Psychiatric Association, 2000) as determined by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Additionally, a score of 40 or higher on the clinician-rated Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984) was required for inclusion. Healthy control participants did not meet criteria for any DSM-IV-TR diagnosis as assessed in the K-SADS-PL interview.

Exclusion criteria included risk factors for seizure or contraindication to TMS (personal history of seizure disorder, unprovoked seizures, febrile seizures, intracranial tumor, or neurosurgery; family history of epilepsy; implanted metal device or metal fragments; or unstable medical conditions). These exclusion criteria were reviewed and confirmed by administration of the TMS Adult Safety Screen (Keel et al., 2001).

2.3 Procedures

2.3.1 TMS Procedures—Participants underwent single-pulse and paired-pulse transcranial magnetic stimulation (TMS) to obtain measures of cortical inhibitory and excitatory functioning. Surface electromyography (EMG) readings from the abductor pollicis brevis (APB) muscle were obtained while TMS stimulation was applied to the corresponding region of the contralateral primary motor cortex. The procedure was repeated for the opposite hemisphere. Participants remained seated throughout the procedure and wore earplugs for comfort and noise safety.

A Magstim 200 magnetic stimulator device (Magstim Co. Ltd., Whitland, Wales, UK) with a figure-of-eight coil (diameter = 70 mm for each loop) was placed tangentially over the scalp overlying the primary motor cortex. The optimal coil position was determined by moving the coil in 1-cm increments while delivering magnetic pulses and observing for maximal contraction of the contralateral APB. Once the optimal position was located, the resting motor threshold (RMT) was determined by increasing pulse intensity until a motor evoked potential (MEP) of at least 50 microvolts was observed in the APB EMG reading in five out of ten trials. After the RMT was established, a series of three other TMS measures was obtained (see Figure 1).

In this study, CSP was measured by surface EMG of the APB following single TMS pulses at 140% of the RMT to the contralateral primary motor cortex while the participant maintained tonic contraction of the APB at 20 percent of maximum contraction, as measured by a hand-held dynamometer. Ten trials were performed bilaterally, and CSP duration values were averaged for each hemisphere.

For the paired-pulse TMS measures (SICI and ICF), a subthreshold (80% of RMT) conditioning stimulus was delivered to the primary motor cortex, followed by a suprathreshold test stimulus (calibrated to produce an MEP with peak-to-peak amplitude in the range of 0.5 to 1.5 millivolts, measured by surface EMG in the contralateral APB). MEP amplitude following the test stimulus was recorded and was expressed as a ratio of the mean

unconditioned MEP amplitude. The interstimulus interval (i.e., the time between the conditioning and test stimuli) was 2 ms and 4 ms for the SICI paradigms. For the ICF paradigm, interstimulus intervals were 10 ms, 15 ms, and 20 ms. Twelve trials at each ISI were performed in each hemisphere in a counterbalanced and randomized manner. Data for each ISI were averaged.

2.4 Measures

2.4.1 Depression Severity—Prior to TMS testing, depression severity was assessed with two scales. The Quick Inventory of Depressive Symptomatology (QIDS-A₁₇-SR) (Bernstein et al., 2010) is a 17-item self-report questionnaire of depressive symptoms completed by the adolescent. The CDRS-R (Poznanski et al., 1984) is a clinician-rated instrument that yields a composite score of depression severity based on both parent and adolescent reports of depressive symptoms. Depression severity was measured in the MDD group as well as the healthy control group to provide a continuous measure of depressive symptom severity across our sample.

2.4.2 Cortical Inhibition—Two TMS measures representing different aspects of GABAergic cortical inhibition are the cortical silent period (CSP) and short-interval intracortical inhibition (SICI). The CSP is an interruption in voluntary muscular contraction induced by a single TMS pulse to the contralateral primary motor cortex. Although the first phase (approximately 50 milliseconds) of the CSP is thought to represent contributions by inhibitory mechanisms in both cortical and spinal neurons, the latter portion has been shown to relate exclusively to GABA_B receptor-mediated inhibition in the stimulated cortex; thus, CSP duration is a putative index of intracortical GABA_B-mediated inhibitory neurotransmission (Wolters, 2008). In contrast, SICI measures are induced by paired TMS pulses applied to the motor cortex. A subthreshold (80% of resting motor threshold [RMT]) conditioning stimulus is followed by a suprathreshold test stimulus after a brief (typically 2–5 ms) interstimulus interval. Previous work has shown the SICI to represent GABA_A receptor-mediated cortical inhibition (Hanajima, 2008; Ziemann, 2004).

2.4.3 Cortical Excitability—Intracortical facilitation (ICF) is a TMS paradigm that pairs a subthreshold (80% of RMT) conditioning stimulus with a subsequent suprathreshold test stimulus, with an interstimulus interval of 10–15 ms. This produces a facilitated (i.e., higher in amplitude compared to baseline) motor evoked potential (Hanajima, 2008). Previous electrophysiologic studies have concluded that ICF results from facilitation in the motor cortex rather than spinal neurons (Ziemann et al., 1996b), and related pharmacologic studies have implicated the role of *N*-methyl-D-aspartate glutamate (NMDA) receptors in the ICF phenomenon (Ziemann et al., 1998). As such, ICF is thought to index NMDAR-mediated excitatory neurotransmission in the cortex (Hanajima, 2008).

2.5 Statistical Analysis

Continuous variables of demographics and baseline clinical characteristics of the sample were described with means (SDs). Categorical variables were described with frequencies and percentages. The Spearman rank-order correlation coefficient (ρ) was used to examine the relationship between TMS measures of cortical inhibition and excitability (CSP, SICI,

RMT, and ICF) and depression severity (QIDS-A₁₇-SR and CDRS-R). The correlation analysis was implemented in the overall sample of all participants (combined healthy controls and MDD participants) and then separately in depressed youth and healthy controls. Statistical analyses were performed using JMP 10.0.0 software (SAS Institute, Inc., Cary, NC, USA). Significance was set at an α level of 0.05 (two-tailed). In the interest of detecting preliminary signals for hypothesis generation, the raw (unadjusted) p -values were interpreted; however, for the interested reader, we also report the adjusted p -values using the False Discovery Rate (FDR) procedure (Benjamini and Hochberg, 1995).

3. Results

3.1 Participant Characteristics

Forty-six participants between the ages of 9 and 17 years were enrolled and tested. The control group consisted of 22 adolescents (11 male, 11 female) who did not meet criteria for any DSM-IV-TR diagnosis. The MDD group consisted of 24 adolescents (10 male, 14 female) meeting criteria for a major depressive episode at the time of the study; the mean episode duration was 10.9 ± 9.7 months (range 1–48 months). The MDD and healthy control groups did not differ in age, sex, or handedness. A full report of demographic characteristics, as well as group means of measures of depression severity and TMS measures of cortical inhibition and excitability, is presented in our previous study with this same sample of participants (Croarkin et al., 2013).

3.2 Overall Sample of Participants

3.2.1 Depression Severity and Cortical Inhibition Correlations—An inverse relationship between CSP and both depression severity measures was observed (Table 1). The adolescent self-report measure (QIDS-A₁₇-SR) scores showed significant negative correlations with CSP duration in the left hemisphere ($\rho = -0.33$, $p = 0.031$) and right hemisphere ($\rho = -0.42$, $p = 0.004$). The CDRS-R summary scores also demonstrated negative correlations with CSP duration, reaching significance in the right hemisphere ($\rho = -0.35$, $p = 0.021$) but not in the left hemisphere ($\rho = -0.18$, $p = 0.260$). The short-interval intracortical inhibition (SICI) amplitude did not demonstrate significant correlation with either depression severity measure, with the exception of the SICI in the right hemisphere at the 4-ms ISI ($\rho = -0.30$, $p = 0.042$).

3.2.2 Depression Severity and Cortical Excitability Correlations—No significant correlations were observed between measures of depression severity and TMS measures of cortical excitability (RMT, ICF-10, -15, and -20) in either hemisphere (see Table 1).

3.3 Sample of Healthy Control Participants

3.3.1 Depression Severity and Cortical Inhibition Correlations—In the healthy control group, no significant correlations were observed between measures of depression severity and TMS measures of cortical inhibition (CSP duration, SICI-2, or SICI-4) in either hemisphere (Table 2).

3.3.2 Depression Severity and Cortical Excitability Correlations—There was no significant relationship between the CDRS-R and TMS measures of cortical excitability (RMT; ICF-10, -15, and -20) in either hemisphere. However, the QIDS-A₁₇-SR score did demonstrate a negative relationship with ICF amplitude (see Table 2). At the 10-ms ISI, ICF revealed a significant negative correlation with the QIDS-A₁₇-SR score in the right hemisphere ($\rho = -0.44$, $p = 0.044$), but not in the left hemisphere ($\rho = -0.40$, $p = 0.079$). At 15 ms, the QIDS-A₁₇-SR score and ICF amplitude also showed a significant negative correlation in the right hemisphere ($\rho = -0.48$, $p = 0.026$), but not in the left hemisphere ($\rho = -0.38$, $p = 0.096$). For the 20-ms ISI, the QIDS-A₁₇-SR score showed a significant inverse relationship with ICF amplitude in the left hemisphere ($\rho = -0.63$, $p = 0.003$), but not in the right hemisphere ($\rho = -0.04$, $p = 0.859$). No significant correlations were observed in either hemisphere between the depression severity measures and the resting motor threshold (RMT).

3.4 Sample of Depressed Participants

3.4.1 Depression Severity and Cortical Inhibition Correlations—The CSP demonstrated an inverse relationship with both measures of depression severity (Table 3). Scores on the adolescent self-report measure (QIDS-A₁₇-SR) demonstrated a significant correlation with the CSP duration for both hemispheres (left hemisphere: $\rho = -0.56$, $p = 0.009$; right hemisphere: $\rho = -0.43$, $p = 0.047$; see Figure 2). CDRS-R composite summary scores also showed an inverse correlation with CSP duration, but it did not reach statistical significance (left hemisphere: $\rho = -0.25$, $p = 0.267$; right hemisphere: $\rho = -0.17$, $p = 0.439$). The short-interval intracortical inhibition (SICI) amplitude did not demonstrate a significant correlation with either depression severity measure at 2-ms or 4-ms interstimulus intervals.

3.4.2 Depression Severity and Cortical Excitability Correlations—For the intracortical facilitation (ICF) paradigms, several significant correlations were demonstrated between depression severity measures and ICF amplitude (Table 3; Figure 3). At the 10-ms interstimulus interval (ICF-10), the QIDS-A₁₇-SR score had a significant negative correlation with ICF amplitude in the left hemisphere ($\rho = -0.46$, $p = 0.035$) but not in the right hemisphere ($\rho = -0.26$, $p = 0.218$). However, the CDRS-R score demonstrated significant correlations with ICF amplitude in both hemispheres (left: $\rho = -0.52$, $p = 0.015$; right: $\rho = -0.44$, $p = 0.031$). For the 15-ms interstimulus interval, the QIDS-A₁₇-SR score demonstrated significant inverse correlations with ICF amplitude in both hemispheres (left: $\rho = -0.53$, $p = 0.014$; right: $\rho = -0.41$, $p = 0.045$), as did the CDRS-R score (left: $\rho = -0.63$, $p = 0.002$; right: $\rho = -0.44$, $p = 0.031$). Neither depression severity measure showed a significant correlation with ICF amplitude in either hemisphere at the 20-ms interstimulus interval (ICF-20). No significant correlations were observed between measures of depression severity and the resting motor threshold (RMT) in either hemisphere.

4. Discussion

To our knowledge, this is the first study to examine TMS-measured inhibitory and excitatory correlates of depression severity in a pediatric population. Furthermore, it adds to

the emerging, but still quite limited, body of literature on noninvasive measures of cortical GABAergic and glutamatergic dysfunction in depressed individuals.

4.1 Cortical Inhibition and Depression Severity

Several previous TMS studies examining the CSP and SICI have shown impaired GABA-mediated cortical inhibition in adults with major depression, albeit with somewhat varying results. Steele and colleagues (2000) demonstrated increased CSP duration in adult patients with MDD compared with a healthy control group that did not differ in other variables such as age, sex, or IQ. Interestingly, in this study the severity of depressive symptoms did not show a significant correlation with CSP duration. In contrast, Lefaucheur et al. (2008) found that left hemisphere CSP duration was reduced compared to the right hemisphere in depressed adult participants; left hemisphere CSP also was significantly shorter in the depressed participants compared to healthy controls, whereas right hemisphere CSP duration did not differ between groups. The authors also noted that SICI was reduced in depressed participants' left hemispheres versus right; SICI was reduced both hemispheres in depressed participants compared to healthy controls, suggesting both global cortical inhibitory deficits in depression as well as a within-participants left-sided predominance, consistent with theories of depression localizing functional deficits to left frontal regions. Bajbouj and colleagues (2006) also examined excitatory and inhibitory measures in depressed participants and healthy controls, finding shortened CSP and reduced SICI in both hemispheres in the depressed group compared to controls. The authors also noted one significant relationship between left hemisphere SICI and depression severity, although other TMS measures did not demonstrate correlations with depression severity measures. Levinson et al. (2010) compared four adult groups of patients with treatment-resistant MDD, MDD patients who were medication-free, medicated MDD patients who were euthymic at the time of testing, and healthy controls. Compared to healthy controls, all three MDD groups demonstrated shorter CSP durations, while the treatment-resistant MDD group showed significantly longer SICI duration compared to other groups. The authors postulated that GABA_B functioning, indicated by the CSP, was dysregulated in major depression but that GABA_A deficits, measured by the SICI, could indicate more severe illness. However, neither cortical inhibition measure was significantly correlated with depression severity in this study.

Our findings, particularly the correlations of CSP duration with depression severity measures, provide, to our knowledge the first evidence of a relationship between TMS-measured GABAergic dysfunction and depression severity in a pediatric population. Although our study did not differentiate participants into severity groups as did Levinson et al. (2010), the correlations between CSP duration and depression severity scores in the overall sample and in the MDD group in our study do suggest that the degree of depressive symptomatology may be related to degree of GABA_B dysfunction, with shorter CSP duration corresponding to more severe depression. Interestingly, the SICI and depression severity relationships were less robust. While this may be the result of a number of factors, including small sample size, one possibility is that adolescents may exhibit differences (compared to adults) in the relative developmental maturity of GABA_A and GABA_B systems. Previous work has demonstrated that significant changes occur in GABAergic and

glutamatergic neurotransmitter systems during development. GABA_A receptors appear to change in their subunit composition, particularly during early development (Duncan et al., 2010), while alterations in GABA_A receptor density occur at varying rates in different brain regions throughout childhood and the adolescent years (Chugani et al., 2001). Other studies have noted significant changes in functional activity of GABA and glutamate receptors during gestation, infancy, and childhood, with some GABAergic neurons displaying paradoxical excitatory roles in early life (Rakhade and Jensen, 2009), further highlighting how these systems are highly dynamic in development.

4.2 Cortical Excitability and Depression Severity

Although prior research has given less attention to the relationship between ICF and depression, Lefaucheur and colleagues (2008) found that ICF was reduced in the left hemisphere compared to right in depressed participants, a difference that was not apparent in the control group. Additionally, left hemisphere ICF (but not right) was reduced in depressed participants compared to controls. However, in their correlational analysis, the authors found that only one depression severity measure demonstrated a significant relationship with left hemisphere ICF. In contrast, Levinson et. al (2010) did not find differences in ICF between groups of treatment-resistant MDD participants, unmedicated MDD patients, medicated euthymic MDD patients, and healthy controls. To our knowledge, no previous studies have demonstrated significant correlational relationships between depression symptom severity and TMS measures of glutamatergic neurotransmission in adolescents, and our findings indicate the most robust evidence to date of these correlations in any age group.

In our study, the direction of the ICF amplitude and depression severity correlations was inverse in both the healthy control group and the MDD group, opposite to what might be expected from the group differences observed in our previous study (Croarkin et al., 2013). The significance of this is unclear and certainly merits further investigation. The fact that the ICF and depression severity correlations were more robust in the depressed group than in healthy controls may simply reflect the minimal variance in depression severity scores within the control group, which could have resulted in a floor effect. However, the fact that the direction of the healthy control correlations matched that of the depressed sample suggests the possibility that even in relatively healthy youth, glutamatergic systems could play a role in the experience of mild, subclinical depressive symptoms. Our findings of numerous significant negative correlations within the depressed group, which were consistent on both depression measures and in both hemispheres and which clustered around the 10- and 15-ms ISIs, suggest the presence of a physiologic process involved in depressive symptomatology. The more robust findings in the MDD group may indicate that glutamatergic neurophysiology becomes dramatically altered during a depressive episode.

4.3 Limitations

The current study has a few limitations. First, this was a small sample, and although notable for being among the first research addressing TMS measures of cortical inhibition and excitability in a child and adolescent population, larger studies should be performed in the future. One strength of this sample, however, was its medication-naïve status, and future

studies should give consideration to maintaining this aspect if feasible in order to avoid the confounding effects of pharmacologic agents with GABAergic and glutamatergic properties, which has been a significant limitation in previous TMS studies in depressed adults (Radhu et al., 2013). Given that the aim of this exploratory study was to detect possible signals of relationships between depression severity and GABAergic and glutamatergic neurotransmitter dysfunction for hypothesis generation, we ultimately elected to interpret the raw (unadjusted) p -values; however, for the interested reader, we also report the adjusted p -values using the False Discovery Rate procedure (Benjamini and Hochberg, 1995). Future hypothesis-driven studies aiming to establish these relationships more definitively should consider implementing the FDR or positive FDR (given the context). If the effect of prolonged depression on GABAergic and glutamatergic systems is cumulative as suggested by prior work (Levinson, et al., 2010), episode duration or number of depressive episodes could impact the degree of cortical inhibitory and excitatory dysfunction. These and other factors related to disease burden should be examined in future studies. Additionally, the changes that occur in GABAergic and glutamatergic systems with development are a potential confound given the broad age range in our study. Previous work has demonstrated inverse relationships between motor threshold and age (Gilbert et al., 2011; Moll et al., 1999), which may be more pronounced in depression (Croarkin et al., 2014). Other considerations for future studies would be to control for effects of sex and menstrual status. While the previous adult literature has found little difference between hemispheres (in relation to handedness) or genders on paired-pulse TMS measures of inhibition and facilitation (Cahn et al., 2003), other studies have indicated a relative cortical facilitation effect during the luteal phase in adult women with premenstrual syndrome (Smith et al., 2003), which is theorized to be related to the activity of neuroactive progesterone metabolites at GABA receptors. These effects, as well as the considerable variation in circulating levels of sex steroids during the adolescent years, should be considered in future work attempting to characterize TMS measures of cortical inhibition and excitability in adolescents.

4.4 Implications

Throughout psychiatry, there is increasing initiative to shift from categorical and phenomenologically-based diagnostic classification systems to ones rooted in the growing body of neurobiological markers and mechanistic research. The National Institute of Mental Health's Research Domain Criteria (RDoC) project has advocated a fundamental shift in how mental disorders are understood and researched, proposing that common genetic, epigenetic, molecular, and neural circuitry mechanisms cut across traditional symptom-based diagnostic categories. This has dramatic implications for the selection of efficacious treatments for mental illnesses and has the potential to yield the more individualized approaches to treatment seen in other disciplines of medicine (Insel and Cuthbert, 2015). Moreover, it is particularly imperative in child and adolescent psychiatry, in which neurobiologic mechanisms of psychiatric illness are less clearly understood and in which diagnosis often is less certain. A dimensional approach to investigating the neurodevelopmental mechanisms of cognitive and emotional processes will be essential in advancing our knowledge of how mental illnesses arise in the rapidly-changing brains of young persons (Casey et al., 2014). Ultimately, greater understanding of an individual

child's particular neurochemical and neurophysiologic characteristics will help to distinguish the underlying pathology and to guide the clinician's selection of appropriate pharmacotherapy or psychotherapeutic interventions. Individualized approaches may not only facilitate more rapid selection of efficacious treatments but also mitigate exposure to ineffective treatments with adverse effects. The identification of neurobiological correlates also will help clinicians to assess risk for particular adverse outcomes, such as self-injurious or suicidal behavior, if associations between such behaviors and neurochemical or neurophysiologic measures are demonstrated, giving clinicians additional data-informed tools in assessing and treating adolescents. As a relatively inexpensive and noninvasive means of evaluating neural circuitry functioning, TMS shows great promise for future applications in both clinical assessment and research. The preliminary findings in this study regarding the relationship between cortical GABAergic and glutamatergic dysfunction and depression severity point to an important area of further research in the development of biomarkers of depression severity in children and adolescents.

Acknowledgments

Dr. Lewis was supported by the Mayo Clinic Foundation's Psychiatry and Psychology Small Grant program. Dr. Croarkin was supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) under Award Number K23 MH100266. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research was also supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Dr. Croarkin).

Role of Funding Sources

Grants provided funding for salary support for the research team, participant reimbursement, and TMS equipment. Funding sources had no role in the design and conduct of the study.

Dr. Lewis receives research support from the Mayo Clinic Foundation's Departmental Small Grant Program. Dr. Ameis receives financial support from the O'Brien Scholar's Program, the Ontario Mental Health Foundation New Investigator Fellowship, and the University of Toronto Dean's Fund New Staff Grant. Dr. Husain has received research support from NIH/NIMH, NIDA, NINDS, NIA, the Brain and Behavior Research Foundation, the Stanley Foundation, Cyberonics, Inc., Neuronetics, Inc. (past), St. Jude Medical, Inc. (ANS), Magstim Co. Ltd. (equipment only), Brainsway Ltd., NeoSync, Inc., Alkermes plc, and Corcept Therapeutics, Inc. Dr. Emslie has received research support from NIMH, NCS Pearson, Inc. (previously BioBehavioral Diagnostics), BioMarin Pharmaceutical, Inc., Duke University, Eli Lilly and Co., Forest Laboratories, Inc., GlaxoSmithKline plc, Mylan N.V., and Somerset Pharmaceuticals, Inc.; has served as a consultant for Alkermes plc, Allergan plc, NCS Pearson, Inc. (previously BioBehavioral Diagnostics), Bristol-Myers Squibb Co., Eli Lilly and Co., Forest Laboratories, Inc., GlaxoSmithKline plc, INC Research, LLC, Lundbeck A/S, Merck & Co., Inc., Neuronetics, Inc., Otsuka Pharmaceutical Co., Ltd., Pfizer, Inc., Seaside Therapeutics, LLC, Shire plc, the Texas Department of State Health Services, the University of Miami, Valeant Pharmaceuticals International, Inc., and Wyeth Pharmaceuticals; and was on the Speakers Bureau for Forest Laboratories, Inc. Dr. Daskalakis has received research and equipment in-kind support for an investigator-initiated study through Brainsway Ltd.; he also has served on the advisory board for F. Hoffmann-La Roche Ltd. and Merck & Co., Inc. and has received speaker support from Eli Lilly and Co. Dr. Croarkin has received research grant support from Pfizer, Inc., NIMH (K23 MH100266), the Brain and Behavior Research Foundation, and the Mayo Clinic Foundation. He has served as a site subprincipal or principal investigator (without additional compensation) for Eli Lilly and Co., Forest Laboratories, Inc., Merck & Co., Inc., and Pfizer, Inc.; has received equipment support (disposable Senstar shields) from Neuronetics, Inc.; and receives supplies and genotyping services from AssureRx Health, Inc. for an investigator-initiated study.

Abbreviations

APB	abductor pollicis brevis
CDRS-R	Children's Depression Rating Scale-Revised

CSP	cortical silent period
DSM-IV-TR	<i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision</i>
EMG	electromyography
FDR	False Discovery Rate
GABA	gamma-aminobutyric acid
GABA_A	gamma-aminobutyric acid [receptor], type A
GABA_B	gamma-aminobutyric acid [receptor], type B
ICF	intracortical facilitation
ICF-10	intracortical facilitation at 10-ms interstimulus interval
ICF-15	intracortical facilitation at 15-ms interstimulus interval
ICF-20	intracortical facilitation at 20-ms interstimulus interval
ISI	interstimulus interval
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version
MEP	motor evoked potential
MDD	major depressive disorder
NMDA	<i>N</i> -methyl-D-aspartate
NMDAR	<i>N</i> -methyl-D-aspartate receptor
QIDS-A₁₇-SR	Quick Inventory of Depressive Symptomatology, Adolescent Version, Self-Report
RDoC	Research Domain Criteria
RMT	resting motor threshold
SICI	short-interval intracortical inhibition
SICI-2	short-interval intracortical inhibition at 2-ms interstimulus interval
SICI-4	short-interval intracortical inhibition at 4-ms interstimulus interval
TMS	transcranial magnetic stimulation

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Highlights

Neurophysiologic correlates of depression severity were examined via TMS.

The sample consisted of unmedicated youth with major depression and healthy controls.

Depression severity showed an association with inhibitory (GABAergic) TMS measures.

Excitatory (glutamatergic) measures showed associations with depression severity.

The majority of significant relationships were observed in the depressed group.

Figure 1.

Electromyography of TMS Measures of Cortical Excitability and Inhibition [Caption]

Electromyography of single- and paired-pulse TMS paradigms. The resting motor threshold (RMT; **a**) is established when a single TMS pulse of sufficient intensity results in a motor evoked potential (MEP). The cortical silent period (CSP; **b**) is exhibited when a single suprathreshold TMS pulse is delivered during a tonic muscle contraction, resulting in a pause of electromyographic activity. Short-interval intracortical inhibition (SICI; **c**) results from paired TMS pulses separated by a brief interstimulus interval (2 ms shown), while intracortical facilitation (ICF; **d**) is seen with paired pulses separated by a longer ISI (20 ms shown).

Figure 2.
Significant Cortical Silent Period and Depression Severity Relationships (Depressed Participants)

Figure 3.
Significant Cortical Excitability and Depression Severity Relationships (Depressed Participants) a. ICF amplitude vs CDRS-R score b. ICF amplitude vs QIDS-A₁₇-SR score

Table 1

Depression Severity and Cortical Inhibition/Cortical Excitability Correlations, Overall Sample of Participants

	CDRS-R		QIDS-A ₁₇ -SR	
	Spearman ρ	p Value (p_{FDR})	Spearman ρ	p Value (p_{FDR})
<i>Cortical Inhibition</i>				
CSP duration (L)	-0.18	0.260 (0.870)	-0.33	0.031 (0.217)
CSP duration (R)	-0.35	0.021 (0.294)	-0.42	0.004 (0.056)
SICI-2 amplitude (L)	-0.08	0.607 (0.955)	-0.19	0.232 (0.464)
SICI-2 amplitude (R)	-0.0003	0.998 (0.998)	-0.04	0.779 (0.952)
SICI-4 amplitude (L)	-0.04	0.791 (0.967)	-0.10	0.530 (0.742)
SICI-4 amplitude (R)	-0.30	0.042 (0.294)	-0.25	0.093 (0.325)
<i>Cortical Excitability</i>				
RMT amplitude (L)	-0.03	0.867 (0.967)	-0.0002	0.999 (0.999)
RMT amplitude (R)	0.03	0.855 (0.967)	0.02	0.911 (0.981)
ICF-10 amplitude (L)	-0.19	0.227 (0.872)	-0.29	0.066 (0.308)
ICF-10 amplitude (R)	-0.12	0.436 (0.872)	-0.13	0.411 (0.711)
ICF-15 amplitude (L)	-0.13	0.435 (0.872)	-0.19	0.229 (0.464)
ICF-15 amplitude (R)	-0.02	0.898 (0.967)	-0.11	0.457 (0.711)
ICF-20 amplitude (L)	-0.13	0.416 (0.872)	-0.23	0.150 (0.420)
ICF-20 amplitude (R)	0.08	0.614 (0.955)	0.04	0.816 (0.952)

Abbreviations: CSP, cortical silent period; (L), left hemisphere; (R), right hemisphere; SICI-2, short-interval intracortical inhibition at 2-ms interstimulus interval; SICI-4, short-interval intracortical inhibition at 4-ms interstimulus interval; RMT, resting motor threshold; ICF-10, intracortical facilitation at 10-ms interstimulus interval; ICF-15, intracortical facilitation at 15-ms interstimulus interval; ICF-20, intracortical facilitation at 20-ms interstimulus interval; p_{FDR} , p -value adjusted using the False Discovery Rate (FDR) procedure.

Table 2

Depression Severity and Cortical Inhibition/Cortical Excitability Correlations, Healthy Control Participants

	CDRS-R		QIDS-A ₁₇ -SR	
	Spearman ρ	p Value (p_{FDR})	Spearman ρ	p Value (p_{FDR})
<i>Cortical Inhibition</i>				
CSP duration (L)	-0.09	0.690 (0.878)	-0.24	0.282 (0.564)
CSP duration (R)	-0.11	0.625 (0.878)	-0.11	0.616 (0.967)
SICI-2 amplitude (L)	0.11	0.646 (0.878)	0.01	0.974 (0.974)
SICI-2 amplitude (R)	0.12	0.615 (0.878)	-0.03	0.898 (0.967)
SICI-4 amplitude (L)	-0.01	0.982 (0.982)	-0.08	0.744 (0.967)
SICI-4 amplitude (R)	0.20	0.393 (0.878)	0.26	0.249 (0.564)
<i>Cortical Excitability</i>				
RMT amplitude (L)	-0.04	0.855 (0.921)	0.04	0.853 (0.967)
RMT amplitude (R)	-0.07	0.767 (0.894)	-0.08	0.710 (0.967)
ICF-10 amplitude (L)	-0.10	0.689 (0.878)	-0.40	0.079 (0.268)
ICF-10 amplitude (R)	-0.30	0.189 (0.878)	-0.44	0.044 (0.205)
ICF-15 amplitude (L)	-0.22	0.354 (0.878)	-0.38	0.096 (0.268)
ICF-15 amplitude (R)	-0.36	0.114 (0.798)	-0.48	0.026 (0.182)
ICF-20 amplitude (L)	-0.41	0.073 (0.798)	-0.63	0.003 (0.042)
ICF-20 amplitude (R)	0.24	0.301 (0.878)	-0.04	0.859 (0.967)

Abbreviations: CSP, cortical silent period; (L), left hemisphere; (R), right hemisphere; SICI-2, short-interval intracortical inhibition at 2-ms interstimulus interval; SICI-4, short-interval intracortical inhibition at 4-ms interstimulus interval; RMT, resting motor threshold; ICF-10, intracortical facilitation at 10-ms interstimulus interval; ICF-15, intracortical facilitation at 15-ms interstimulus interval; ICF-20, intracortical facilitation at 20-ms interstimulus interval; p_{FDR} , p -value adjusted using the False Discovery Rate (FDR) procedure.

Table 3

Depression Severity and Cortical Inhibition/Cortical Excitability Correlations, Depressed Participants

	CDRS-R		QIDS-A ₁₇ -SR	
	Spearman ρ	p Value (p_{FDR})	Spearman ρ	p Value (p_{FDR})
<i>Cortical Inhibition</i>				
CSP duration (L)	-0.25	0.267 (0.463)	-0.56	0.009 (0.098)
CSP duration (R)	-0.17	0.439 (0.558)	-0.43	0.047 (0.131)
SICI-2 amplitude (L)	-0.22	0.331 (0.463)	-0.39	0.079 (0.184)
SICI-2 amplitude (R)	0.01	0.976 (0.976)	0.03	0.876 (0.876)
SICI-4 amplitude (L)	-0.26	0.262 (0.463)	-0.28	0.218 (0.381)
SICI-4 amplitude (R)	-0.23	0.272 (0.463)	-0.14	0.529 (0.725)
<i>Cortical Excitability</i>				
RMT amplitude (L)	-0.26	0.235 (0.463)	-0.19	0.377 (0.586)
RMT amplitude (R)	-0.06	0.798 (0.859)	-0.09	0.683 (0.786)
ICF-10 amplitude (L)	-0.52	0.015 (0.105)	-0.46	0.035 (0.131)
ICF-10 amplitude (R)	-0.44	0.031 (0.108)	-0.26	0.218 (0.381)
ICF-15 amplitude (L)	-0.63	0.002 (0.028)	-0.53	0.014 (0.098)
ICF-15 amplitude (R)	-0.44	0.031 (0.108)	-0.41	0.045 (0.131)
ICF-20 amplitude (L)	-0.07	0.757 (0.859)	-0.08	0.730 (0.786)
ICF-20 amplitude (R)	-0.21	0.326 (0.463)	-0.12	0.570 (0.725)

Abbreviations: CSP, cortical silent period; (L), left hemisphere; (R), right hemisphere; SICI-2, short-interval intracortical inhibition at 2-ms interstimulus interval; SICI-4, short-interval intracortical inhibition at 4-ms interstimulus interval; RMT, resting motor threshold; ICF-10, intracortical facilitation at 10-ms interstimulus interval; ICF-15, intracortical facilitation at 15-ms interstimulus interval; ICF-20, intracortical facilitation at 20-ms interstimulus interval; p_{FDR} , p -value adjusted using the False Discovery Rate (FDR) procedure.