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Research report

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.
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-A_{17}-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-A_{17}-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-A_{17}-SR and right ICF-10; QIDS-A_{17}-SR and right ICF-15; and QIDS-A_{17}-SR and left ICF-20. Among depressed participants, significant negative correlations were observed between QIDS-A_{17}-SR and bilateral CSP; CDRS-R and bilateral ICF-10; CDRS-R and bilateral ICF-15; QIDS-A_{17}-SR and left ICF-10; and QIDS-A_{17}-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.

Abbreviations: APB, abductor pollicis brevis; CDRS-R, Children's Depression Rating Scale-Revised; CSP, cortical silent period; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; 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, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; QIDS-A_{17}-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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1. Introduction

Depression is a common condition in pediatric populations and is a significant public health concern. Among adolescents in the United States, 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, 2015). 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, 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 anesthetic 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 non-invasively 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, 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