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Evidence for Pretreatment LICI Deficits Among Depressed Children and Adolescents With Nonresponse to Fluoxetine

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ABSTRACT

Background: Research suggests that alterations in gamma-aminobutyric acid receptor functioning have a role in depression. Paired-pulse transcranial magnetic stimulation (TMS) paradigms are noninvasive measures of cortical inhibitory and excitatory circuits.
Objective/hypothesis: The present study examined pretreatment short-interval intracortical inhibition (SICI), long-interval cortical inhibition (LICI), and intracortical facilitation (ICF) in children and adolescents with major depressive disorder who were initiating fluoxetine treatment. The primary objective was to examine the relationship of these measures with subsequent treatment response. It was hypothesized that alterations in pretreatment GABA and glutamate mediated neurotransmission, would be associated with fluoxetine nonresponse.

Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CGI-I, Clinical Global Impression-Improvement; GABA, gamma-aminobutyric acid; ICF, intracortical inhibition; ISI, interstimulus interval; LICI, long-interval cortical inhibition; LS, least squares; MDD, major depressive disorder; SICI, short-interval intracortical inhibition; SSRI, selective serotonin reuptake inhibitor; TMS, transcranial magnetic stimulation.

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

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Adolescents
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Methods: Sixteen children and adolescents with major depressive disorder underwent paired-pulse TMS testing before beginning fluoxetine treatment. Response was prospectively characterized by scores of 1 or 2 on the Clinical Global Impression Scale and less than 40 on the Children's Depression Rating Scale-Revised after 6 weeks of fluoxetine treatment (20–40 mg/day).
Results: Eight patients responded to treatment. Least-squares mean LICI values were consistently higher bilaterally for treatment nonresponders. Higher LICI values indicate less inhibition and impaired $GABA_B$ functioning. There was no significant effect of treatment response on the measures of SICI and ICF.
Conclusions: Our findings suggest that deficits in pretreatment $GABA_B$ may be related to fluoxetine nonresponse in depressed youth. This is congruent with prior work demonstrating that $GABA_B$ interneurons have serotonergic input and antidepressants modulate $GABA_B$ receptors. These findings also show that TMS paradigms have utility in studying the neurophysiology and treatment of childhood mood disorders.
Registrations: Cortical Excitability and Inhibition in Children and Adolescents With Major Depressive Disorder, http://www.clinicaltrials.gov/ct2/show/NCT00896090?term=cortical+excitability+and+inhibition&rank=2, NCT00896090; Sequential Treatment of Pediatric MDD to Increase Remission and Prevent Relapse, http://www.clinicaltrials.gov/ct2/show/NCT00612313?term=Sequential+Treatment+and+MDD&rank=1, NCT00612313.

Introduction

Prior research implicates gamma-aminobutyric acid (GABA) in the pathophysiology of major depressive disorder (MDD) [1,2]. Numerous imaging [3], neuropathologic [4], and transcranial magnetic stimulation (TMS) [5,6] studies suggest that adults with MDD have impaired GABA-mediated neurotransmission. Work with children and adolescents is nascent, as demonstrated with a recent proton magnetic resonance spectroscopy study by Gabbay and colleagues [7] that examined GABA levels in the anterior cingulate cortex of adolescents with MDD. In this instance, adolescents with MDD demonstrated significantly lower levels of GABA in the anterior cingulate cortex than healthy control subjects. Also, GABA levels were negatively correlated with ratings of anhedonia.

Preclinical work also indicates that alterations in $GABA_A$- and $GABA_B$-mediated neurotransmission have a role in depressive symptoms and in clinical response to selective serotonin reuptake inhibitors (SSRIs) [8,9]. Fluoxetine in particular may potentiate GABAergic neurotransmission [10,11]. One prior study in depressed adults demonstrated that 2 months of SSRI treatment increased cortical GABA levels, as assessed with proton magnetic resonance spectroscopy [12]. At present, little is known regarding GABAergic synaptic activity in children and adolescents with MDD and in the context of treatment with SSRIs.

TMS is a neuropsychiatric probe that noninvasively measures the activity of cortical interneurons and pyramidal cells [13,14]. Prior studies with healthy participants have showed that in paired-pulse TMS, a conditioning stimulus delivered to the motor cortex produces inhibitory or excitatory changes based on the intensity of the conditioning stimulus and the interstimulus interval between the conditioned and test stimulus [15]. This response is quantified with electromyography measures of motor-evoked potentials [16]. Short-interval intracortical inhibition (SICI) is measured with a subthreshold conditioning stimulus followed by a suprathreshold test pulse and an interstimulus interval (ISI) of 1–5 ms. During Intracortical facilitation (ICF) measures, a subthreshold conditioning stimulus and suprathreshold test stimulus are applied with an ISI of 10–20 ms. Long-interval cortical inhibition (LICI) is a paired-pulse paradigm (Fig. 1) that is elicited when suprathreshold conditioning and suprathreshold test stimuli are delivered to the motor cortex with interstimulus intervals between 50 and 200 ms [17,18]. Prior work indicates that SICI is a measure of $GABA_A$ mediated neurotransmission and LICI is mediated by slow $GABA_B$ inhibitory postsynaptic potentials [19]. This was demonstrated in studies in which $GABA_A$ agonists potentiate SICI [20] and $GABA_B$ agonists, potentiate LICI [21,22]. The durations and intensities of SICI and LICI are also consistent with those demonstrated in-vivo of respective $GABA_A$ and $GABA_B$ inhibitory postsynaptic potentials [18,19]. Finally, LICI also attenuates measures of $GABA_A$, such as SICI [18,23,24]. This latter line of evidence parallels preclinical work finding that $GABA_B$-mediated tone presynaptically inhibits cortical interneurons [25,26]. Similar pharmacologic [27] and neurophysiological [28] studies suggest that ICF indexes glutamatergic neurotransmission.

Two prior studies of cortical inhibition demonstrated $GABA_A$ and $GABA_B$ deficits in adults with MDD [5,6]. Both reports suggest that $GABA_B$ neurophysiologic deficits are intimately linked with the pathophysiologic factors of adult MDD. Prior work suggests that SSRIs increase cortical GABA concentrations [12]. Therefore markers of GABA mediated neurotransmission such as SICI and LICI may predict treatment response with these medications. To our knowledge no study has examined the relationship between paired-pulse TMS measures and treatment response to fluoxetine or other SSRIs in depressed youth [29,30]. Thus, the aim of the present study was to measure pretreatment SICI, LICI, and ICF in medication-naïve children and adolescents with MDD and examine their relationships with SSRI treatment response. We hypothesized that inhibitory or excitatory deficits would be associated with nonresponse to fluoxetine.

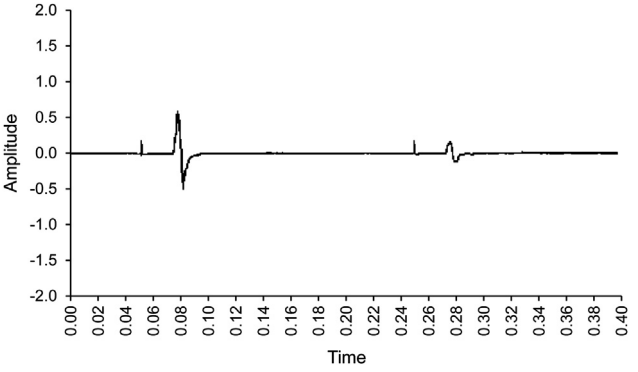

Figure 1. Long-interval cortical inhibition (LICI) is a paired-pulse transcranial magnetic stimulation paradigm in which 2 suprathreshold stimulations are applied to the motor cortex with 1 coil and an interstimulus interval of 50–200 ms. This application results in cortical inhibition as shown by a decrease in the amplitude of the motor evoked potential compared to a test stimulus alone.