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Transcranial magnetic stimulation potentiates glutamatergic neurotransmission in depressed adolescents

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ABSTRACT

Abnormalities in glutamate neurotransmission may have a role in the pathophysiology of adolescent depression. The present pilot study examined changes in cortical glutamine/glutamate ratios in depressed adolescents receiving high-frequency repetitive transcranial magnetic stimulation. Ten adolescents with treatment-refractory major depressive disorder received up to 30 sessions of 10-Hz repetitive transcranial magnetic stimulation at 120% motor threshold with 3000 pulses per session applied to the left dorsolateral prefrontal cortex. Baseline, posttreatment, and 6-month follow-up proton magnetic resonance spectroscopy scans of the anterior cingulate cortex and left dorsolateral prefrontal cortex were collected at 3 T with 8-cm^3 voxels. Glutamate metabolites were quantified with 2 distinct proton magnetic resonance spectroscopy sequences in each brain region. After repetitive transcranial magnetic stimulation and at 6 months of follow-up, glutamine/glutamate ratios increased in the anterior cingulate cortex and left dorsolateral prefrontal cortex with both measurements. The increase in the glutamine/glutamate ratio reached statistical significance with the TE-optimized PRESS sequence in the anterior cingulate cortex. Glutamine/glutamate ratios increased in conjunction with depressive symptom improvement. This reached statistical significance with the TE-optimized PRESS sequence in the left dorsolateral prefrontal cortex. High-frequency repetitive transcranial magnetic stimulation applied to the left dorsolateral prefrontal cortex may modulate glutamate neurochemistry in depressed adolescents.

1. Introduction

Major depressive disorder (MDD) frequently presents in adolescence and is often recalcitrant to treatment (Brent, 2009) which leads to substantial morbidity, mortality, and a societal financial burden (Blazer et al., 1994; Greenberg et al., 2015). Suicide is a leading cause of death in adolescents and a stark reminder that the current mechanistic understanding of depression is underdeveloped (Vitiello et al., 2011). Unfortunately, antidepressant medications, cognitive-behavioral therapy, and combined treatment are either ineffective or have minimal durability for most depressed adolescents (March et al., 2009).

Noninvasive brain stimulation technologies such as repetitive transcranial magnetic stimulation (rTMS) may have promise as enduring therapeutic interventions in young people (Donaldson et al., 2014). Prior research has shown that rTMS applied to the left dorsolateral prefrontal cortex (L-DLPFC) is a safe and effective treatment for MDD in adults who fail to benefit from antidepressant medications (O'Reardon et al., 2007; George et al., 2010). Initial open-label studies of rTMS for MDD in adolescents suggest that it may be effective and well-tolerated in younger people, as well (Donaldson et al., 2014). Although rTMS treatment has US Food and Drug Administration clearance for adults, little is known about its mechanism of action and target engagement, especially in adolescents. Further research focused on

Abbreviations: ACC, anterior cingulate cortex; CDRS-R, Children's Depression Rating Scale-Revised; CSF, cerebrospinal fluid; FAST, Fourier acquired steady state; FDR, false discovery rate; Gln, glutamine; Glu, glutamate; ^{1}H-MRS, proton magnetic resonance spectroscopy; ICC, intraclass correlation coefficient; L-DLPFC, left dorsolateral prefrontal cortex; LS, least squares; MDD, major depressive disorder; MRI, magnetic resonance imaging; PRESS, Point resolved spectroscopy; SPGR, spoiled gradient recall; rTMS, repetitive transcranial magnetic stimulation; TE, echo time; TR, repetition time

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understanding the underlying pathophysiology of MDD and how rTMS changes a patient's underlying neurophysiology would facilitate precision medicine approaches to brain stimulation treatments.

Glutamate (Glu) is the primary excitatory neurotransmitter, with roles in neurogenesis, synaptogenesis, neuronal migration, cognition, learning, and memory. Following release into the synaptic cleft, Glu is taken up by adjacent astrocytes and converted to glutamine (Gln) which is then transported back to the neuron. The glutamate–glutamine neurotransmitter recycling system is essential for normal neurotransmission (Yuksel and Ongur, 2010) and drives a large fraction of cerebral oxidative metabolism.

Prior research implicates dysregulated glutamatergic neurotransmission in mood disorders (Krystal et al., 2002; Sanacora et al., 2012) and suggests that rTMS may modulate glutamatergic circuitry (Michael et al., 2003). Initial preclinical (Yue et al., 2009) and clinical work (Michael et al., 2003) suggests that multiple sessions of rTMS increase cortical Glu concentrations in the brain.

Many previous proton magnetic resonance spectroscopy (^{1}H-MRS) studies have examined Glu+Gln (so-called Glx) levels in psychiatric disorders, while contemporary studies at higher field strength (3 T and above) have been able to separately measure Glu and Gln. While it is relatively easy to quantify brain Glu (in part due to its higher concentration of approximately 10 mM), accurate measurement of brain Gln remains difficult due to its relatively low brain concentration (estimated at 2–4 mM) and large spectral overlap with other brain metabolites (Hancu and Port, 2011). To mitigate this measurement difficulty and improve sensitivity for detecting glutamate-glutamine cycle dysfunction, recently investigators have used the Gln/Glu ratio (Brennan et al., 2010; Ongur et al., 2011) or the Glu/Gln ratio (Hermann et al., 2012) for detecting neurotransmission abnormalities in patients with psychiatric disorders.

In this study, we assumed that depressed adolescents have glutamate–glutamine cycle dysfunction. The study objective was to examine changes in Gln/Glu ratios in the anterior cingulate cortex and left dorsolateral prefrontal cortex of depressed adolescents receiving high-frequency rTMS. We hypothesized that the Gln/Glu ratio would increase over time as Gln levels would increase and Glu levels would stay the same or decrease following treatment (Yuksel and Ongur, 2010). We also hypothesized that this change would relate to symptom improvement.

2. Methods

2.1. Participants

Participants were recruited and enrolled from the Mayo Clinic Mood Disorders Clinic for this prospective, open-label study of rTMS. The patient group consisted of 10 adolescents aged 13–17 years with treatment-refractory MDD. Parents provided informed consent and adolescents provided informed assent. Adolescents were evaluated and monitored by a child and adolescent psychiatrist for the duration of the study. Baseline assessments to determine eligibility included a semistructured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Geller et al., 2001), review of Diagnostic and Statistical Manual of Mental Disorders Text Revision, Fourth Edition criteria for MDD (American Psychiatric Association, 2000), and a Children's Depression Rating Scale-Revised (CDRS-R) assessment (Poznanski et al., 1984). A CDRS-R symptom severity score of 40 or greater was required for inclusion. All participants had at least 1 prior failed trial of antidepressant medications in the current depressive episode on the basis of Antidepressant Treatment History Form (Sackeim, 2001) standards. Participants received a stable dose of an antidepressant medication for the duration of the study. Participants with secondary comorbid conditions such as anxiety or attention deficit/hyperactivity disorder were eligible for enrollment. Patients with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, substance abuse, substance dependence, somatoform disorder, obsessive–compulsive disorder, posttraumatic stress disorder, eating disorder, intellectual disability, or pervasive developmental disorders were excluded. Study procedures were reviewed and approved by the Mayo Clinic Institutional Review Board before enrollment of the first participant.

2.2. rTMS technique

The *abductor pollicis brevis* site on the motor cortex was identified with standard procedures, as published elsewhere (O'Reardon et al., 2007; George et al., 2010). The resting motor threshold was determined at baseline and after every 10 sessions of rTMS for dosing. The L-DLPFC treatment site was identified with magnetic resonance imaging (MRI) under the supervision of a neuroradiologist (J.D.P.). Treatment sessions were delivered with a Neuronetic Neurostar Therapy System (Neuronetics Inc.). Stimulation was applied to the L-DLPFC at 120% motor threshold and 10 Hz frequency. Stimulus trains were 4 s and intertrain intervals were 26 s, with 3000 pulses delivered during every session. Participants were offered the opportunity to complete up to 30 treatment sessions over 6–8 weeks. Posttreatment ^{1}H-MRS was performed after completion of or upon exit from the treatment portion of the study. As a result, posttreatment ^{1}H-MRS was performed 6 weeks after baseline in 4 participants and 8 weeks after baseline in 6 participants.

2.3. MRI and ^{1}H-MRS acquisition

Total scan time for MRI was 1 h with a GE 3 T Discovery 750 MRI scanner with 22.1 software and an 8-channel head coil. The axial plane was landmarked in all subjects at the center of the forehead, 1 cm above the eyebrows to standardize head position from scan to scan. The forehead was affixed with adhesive tape to the MR bed, and neck support was provided as needed. A neuroradiologist reviewed baseline and posttreatment structural MRI data for potential exclusionary head and brain pathology.

A FAST 3D SPGR sequence was used to acquire volumetric data for cerebrospinal fluid (CSF) correction (axial acquisition; repetition time [TR]=12.6 ms, echo time [TE]=5.6 ms, flip angle=15°, voxel dimensions=$0.49 \times 0.49 \times 1.5$ mm^3). Voxel positioning followed a systematic approach during all scans (Fig. 1). For the midline anterior cingulate cortex (ACC) voxel, a reference slice was taken from an axial cut approximately 1 cm above the genu of the corpus callosum, demonstrating a continuous view of the anterior and posterior horns of the lateral ventricles. On this reference image, an 8-cm^3 voxel ($2 \times 2 \times 2$ cm^3) of predominantly gray (prefrontal) matter was centered on the frontal interhemispheric fissure. The posterior margin of the voxel was placed immediately anterior to the genu of the corpus callosum in an area corresponding to the pregenual ACC (Brodmann area 24a, 24b, and 32), as described by Vogt and Vogt (Vogt and Vogt, 2003). For the left dorsolateral prefrontal cortex voxel (L-DLPFC), a reference coronal oblique localizer slice was positioned on the sagittal anatomical images such that it was positioned perpendicular to the average plane of the corpus callosum, and the posterior margin of the slice was located immediately anterior to the anterior-most portion of the genu of the corpus callosum. On this reference image, an 8-cm^3 voxel ($2 \times 2 \times 2$ cm^3) encompassing the L-DLPFC was placed such that: (1) the superolateral corner of the voxel abutted, but did include, the skull, (2) the medial margin of the voxel excluded the