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INTERNATIONAL POST DOCTORAL RESEARCH FELLOWSHIP PROGRAMME

FINAL REPORT

TITLE OF THE RESEARCH : **Glutamatergic and GABAergic Biomarkers in rTMS for Adolescent Depression**

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GENERAL INFORMATION

RESEARCH TITLE	Glutamatergic and GABAergic Biomarkers in rTMS for Adolescent Depression
RESEARCHER NAME	Dicle Buyuktaskin Tuncturk
RESEARCH FIELD	Child and Adolescent Psychiatry/ Medicine/Health
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Final Report Format:

1. Introduction

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation technique that is commonly used for the treatment of depression. The mechanism of TMS involves the activation of neurons through electrical currents induced by magnetic fields. High frequency (≥1 Hz) TMS is thought to induce a long-term potentiation (LTP)-like activity resulting in excitation of neurons and low frequency (1 Hz) TMS is thought to induce long-term depression (LTD)-like activity resulting in inhibition of neuron. High frequency TMS to the left DLPFC is the most commonly applied protocol and stimulation intensities change from 80 to 120 % of the motor threshold in minors with MDD.

Imbalances in GABAergic and glutamatergic tone play a key role in depression. These neurotransmitters can influence the variability of depression symptoms and treatment response. TMS collects brain specific measures such as intracortical facilitation (ICF), short interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP). ICF, SICI, LICI, and CSP are measures of GABAergic and glutamatergic tone. This project aimed to perform an effectiveness and target validation trial of 1 Hz vs. 10 Hz rTMS with a randomized, biomarker-stratified design. The participants received 6 weeks (30 sessions) of TMS treatment in the first phase of the project. Based on randomization participants either received sessions of 1 Hz rTMS at 120 % motor threshold

(MT) with 2400 continuous pulses or 10 Hz rTMS at 120 % MT with 4 seconds on and 36 seconds off for 2400 pulses. Both 1 Hz and 10 Hz rTMS sessions were delivered to the left dorsolateral prefrontal cortex (LDLPFC). Phase II is for participants who did not respond to Phase I treatment and is a biomarker guided, double-blind trial of continuous vs intermittent theta burst stimulation (TBS). TBS applies bursts of 50 Hz repetitive TMS delivered in triplets every 200 milliseconds, either continuously for a total of 2 minutes (cTBS) or intermittently with 2-second bursts repeated every 10 seconds over 570 seconds (iTBS); with a total of 1800 pulses per session. Cortical GABA, glutamate, and glutamine measured with 7 Tesla MRS were collected at baseline and after 6 weeks of TMS treatment in phase II.

Inclusion criteria included the CDRS-R score of ≥ 40, and the current episode of depression ≥ 4 weeks but ≤ 3 years. Patients with comorbidities including psychotic disorders, bipolar disorders, anorexia nervosa, bulimia nervosa, and substance use disorders within the past year; a positive urine drug screen or urine pregnancy test at baseline, use of any concurrent psychotropic medications or prohibited concomitant medications; history of treatment with ECT or TMS therapy, initiation of a new psychotherapeutic treatment or any investigational drug within the past 4 weeks were excluded. Suicide attempt within the previous 6 months that required medical treatment or ≥ 2 attempts in the past 12 months, or has a clear cut plan for suicide and states that he/she cannot guarantee that he/she will inform a family member or call his/her psychiatrist or the investigator if the impulse to implement the plan becomes substantial during the study; or, in the investigator's opinion, is likely to attempt suicide within the next 6 months were among the exclusion criteria.

2. Studies in report terms

I. Term

The optimal dose parameters for TMS interventions targeting suicidal ideation in adolescents remain unknown. This exploratory study examined the impact of 1 Hz and 10 Hz TMS

treatment on suicidal ideation in adolescents with major depressive disorder. Participants aged 12-18 years were randomized to TMS treatments with 1 Hz or 10 Hz frequency over 6 weeks (30 sessions). The Columbia-Suicide Severity Rating Scale was the primary outcome variable. The change in the intensity of suicidal ideation throughout treatment was estimated with ordinal logistic regression models via a Generalized Estimating Equation (GEE) with and without adjustments for the change in depressive symptom severity (The Children's Depression Rating Scale-Revised Total).

II. Term

Irritability is a debilitating, transdiagnostic symptom in adolescents spanning internalizing and externalizing disorders, and early reduction in irritability with antidepressant treatments has been seen as a positive prognostic sign in depression recovery. There are substantial knowledge gaps regarding how TMS treatments impact irritability. This exploratory study sought to investigate the relationship between irritability and depressive symptoms in adolescents with major depressive disorder (MDD) undergoing treatment with two different doses of TMS. A linear mixed model was used to assess the change in irritability (assessed with item 8 on the Children's Depression Rating Scale-Revised) throughout the treatment course, and a logistic regression was implemented to examine the relationship between early (week 4) irritability improvements and a post-treatment Clinical Global Impressions-Improvement (CGI-I) score.

III. Term

We focused on a staged approach to TMS interventions in adolescents with depression. Adolescents (N=6) who did not respond to standard TMS were offered a two-week course of either continuous or intermittent theta burst stimulation (TBS) based on an ICF. A within-subjects linear mixed model analysis of repeated measures was conducted to assess changes in depressive symptoms using the Children's Depression Rating Scale-Revised (CDRS-R).

IV. Term

Interventional psychiatry encompasses a new generation of therapeutics that includes devices delivering brain stimulation through magnetic or electrical fields, infusions, and psychedelic therapeutics. Noninvasive brain stimulation includes modalities such as electroconvulsive therapy, transcranial magnetic stimulation, and transcranial electrical stimulation that are delivered without surgical procedures. Invasive brain stimulation includes modalities such as vagal nerve stimulation and deep brain stimulation that are surgically implanted. In recent decades the study and clinical translation of interventional modalities has grown. We provided an overview of brain stimulation modalities, ketamine/esketamine, and emerging work with psychedelic therapeutics.

3. Research results

The predicted odds of intensity of suicidal ideation significantly decreased over six-weeks of acute TMS treatment for both the 10 Hz TMS group and the 1 Hz TMS group. However, after adjustment for the change in depression severity as a time-varying covariate in the ordinal logistic regression model, the magnitude of the decrease (or predicted odds) in intensity of suicidal ideation over six weeks of acute TMS treatment was attenuated and rendered non-significant for both the 10 Hz and 1 Hz TMS groups. TMS treatment suicidal ideation outcomes were not significantly different between the 10 Hz and 1 Hz TMS groups.

Irritability significantly improved during the course of both 1 Hz and 10Hz treatments in conjunction with overall depression improvement. There was a significant negative (inverse) relationship between early changes in irritability symptoms and post-treatment CGI-I scores in both treatment groups.

Phase II analysis revealed a significant overall improvement in depressive symptoms from baseline to 6-month follow-up with TBS. Significant pairwise comparisons were observed between baseline and week 2, and between baseline and 6-month follow-up. Guiding TBS

based on ICF may offer a feasible and effective approach in adolescents. Further larger trials are warranted to optimize biomarker-guided TBS in the adolescent population.

4. Conclusion and Comments

Low-frequency TMS may be as effective as high-frequency TMS in treating suicidal ideation in adolescents with depression. Notably, 1 Hz TMS may have a favorable tolerability and safety profile for adolescents. Future work should examine precision approaches to dosing TMS in adolescents with suicidal ideation.

We suggest that irritability is an important correlate of disease severity and predictor of treatment response for MDD in adolescents, replicating similar results found in trials using antidepressant medications. Future research will focus on incorporating assessments of irritability into clinical decision making and intervention discovery for transdiagnostic symptoms of irritability in youth and adolescents.

Improved treatment response to TBS in phase II study may reflect the potential impact of individualized variability based on ICF levels. Guiding TBS based on ICF may offer a feasible and effective approach in adolescents. Further larger trials are warranted to optimize biomarker-guided TBS in the adolescent population.

Neuromodulation techniques and novel pharmacologic agents hold promise as alternative add-on treatment options in child psychiatry. Among these, TMS and tDCS are the most studied neuromodulation approaches for adolescents with various psychiatric disorders. Meanwhile, rapid-acting pharmacologic agents are emerging as significant advancements in psychiatry, offering substantial potential for treating psychiatric disorders in children and adolescents. Future research should focus on adapting these interventions for child psychiatry to evaluate their effectiveness and safety in younger populations. While considering ethics, safety, and the risk of drug abuse, it is crucial to access effective treatments for severe and treatment-resistant conditions in youth.

5. Outputs (Publications, presentations, etc.)

- The New Research Poster entitled, "The Clinical Effects of 1 Hz and 10 Hz Transcranial Magnetic Stimulation on Suicidal Ideation in Adolescents With MDD", at AACAP's 2024 Annual Meeting in Seattle, WA, October 14-19, 2024.
- The oral presentation "The Clinical Effects of 1 Hz and 10 Hz Transcranial Magnetic Stimulation On Suicidal Ideation In Adolescents With Major Depressive Disorder" for the annual Research Forum at the June 12, 2024, the Department of Psychiatry & Psychology Grand Rounds.
- Manuscript entitled "Repetitive Transcranial Magnetic Stimulation Frequency Effects on Suicidal Ideation in Adolescents with Major Depressive Disorder" is under review.
- Manuscript entitled "Trajectories of Irritability Improvement in Depressed Adolescents Treated with 1Hz and 10Hz Transcranial Magnetic Stimulation" is under review.
- Manuscript entitled "A Pilot Study of Sequenced TMS and TBS Dosing in Adolescents with Major Depressive Disorder" is under review.
- Book chapter entitled "Other Biological Interventions" is under review.

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