Clinical Protocol:
Medical Device Investigational Plan

Repetitive Transcranial Magnetic Stimulation for Adolescent Depression: Efficacy, Predictive Biomarkers, and Mechanisms

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Funding Sponsor: University of Minnesota Department of Neuroscience MnDrive

Study Product: Brainsway deep TMS Machine

Protocol Number: rTMS

IDE Number: G150132

Version:
Version 1 **-** June 19, 2015
Version 2 – July 15, 2015
Version 3 – August 5, 2015
Version 4 – October 15, 2015
Version 5 – November 12, 2015
Version 6 - March 10, 2016
Version 7 – April 15, 2016
Version 8 – November 30, 2016
Version 9 - May 22, 2017
Version 10- June 19, 2017
Version 11- August 31, 2017
Version 12 – December 18, 2017
Version 12.1 – January 26, 2018
Version 13 – February 07, 2018
Version 14 – March 28, 2018
Version 15 – September 20, 2018
Version 16 – November 05, 2018
Version 17 – February 08, 2019
Version 18 – February 09, 2020
Version 19 – June 11, 2020
Version 20 – September 16, 2020

Version 21 – December 22, 2020
Version 22 – February 17, 2021

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List of Abbreviations

3T	3 Tesla
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Adverse Event
ANT	Attention Network Task
ANOVA	Analysis of Variance
ARC	Ambulatory Research Center
ATR	Antidepressant Treatment Record
BDI-II	Beck Depression Inventory
CVLT-II	California Verbal Learning Test
CDRS-R	Children's Depression Rating Scale - Revised
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions Scale
CMRR	Center for Magnetic Resonance Research
CRF	Case Report Form
CSSRS	Columbia Suicide Severity Rating Scale
CSSRS-SLV	Columbia Suicide Severity Rating Scale – Since Last Visit
DCCS	Dimensional Change Card Sort Task
D-KEFS	Delis-Kaplan Executive Function System
DLPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Revision
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
ECT	Electroconvulsive Therapy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Human Connectome Project
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IDAS	Inventory of Depression and Anxiety Symptoms
IDS	Investigational Drug Services
IRB	Institutional Review Board
K-SADS	Kiddie Schedule of Affective Disorders and Schizophrenia
MADRS	Montgomery-Asberg Depression Scale
MDD	Major Depressive Disorder
MEPa	Motor Evoked Potential Amplitude
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire
RSFC	Resting State Functional Connectivity
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SHAPS	Snaith-Hamilton Pleasure Scale
STAI	State-Trait Anxiety Inventory
TASS	Transcranial Magnetic Stimulation Adult Safety Screening Form

TEPS	Temporal Experience of Pleasure Scale
TRD	Treatment-Resistant Depression
UTox	Urine Toxicology Screen
WASI	Weschler Abbreviated Scale of Intelligence
YMRS	Young Mania Rating Scale

2. Report of prior investigations

Depression is a leading cause of disability and global disease burden.[1] About 25% of all cases first emerge during adolescence,[2] and an adolescent onset predicts poorer psychosocial functioning and higher levels of suicidality.[3–5] The brain undergoes important refinement during adolescence.[6–9] Due to developmental differences, the neural mechanisms underlying disease and treatment response could differ from adults, highlighting the need to study adolescents separately. Unfortunately, about 20% of adolescents with depression do not respond to currently-available treatments.[10–12] adolescents with treatment-resistant depression (TRD) likely have neural abnormalities that are distinct from other patients and that are not alleviated with standard treatments. Novel treatments addressing these early dysfunctions in neural circuitry could restore healthy neurodevelopment during adolescence thereby preventing long-term morbidity and addressing a significant financial burden for society.

Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for TRD in adults. rTMS applies a pulsatile magnetic field to the scalp which painlessly induces electrical currents to the brain.[13] Typically rTMS is applied to the dorsolateral prefrontal cortex (DLPFC), a brain region that is hypoactive in depression.[14] Whereas standard rTMS stimulates superficial (1cm depth) cortical areas, recent advances in rTMS coil technology support stimulation of deeper (5 cm depth)[13] limbic structures that are also relevant to depression.[15] Deep rTMS is FDA-approved for adults with TRD.[16] Unfortunately, although rTMS is generally safe in children and adolescents,[17] research in adolescent depression TRD is far behind. Only two small, open-labeled rTMS studies in adolescent TRD have been conducted, both using standard rTMS, which have suggested 30%[18] and 70%[19] response rates. No randomized, controlled trials (RCTs) of rTMS have yet been conducted adolescent TRD, and no studies have examined deep rTMS in adolescent TRD. To address these gaps, the current study will conduct an open label trial testing deep rTMS in adolescents with TRD.

Additional gaps in neuromodulation research include the need to understand mechanisms underlying clinical response to rTMS and to identify neural biomarkers capable of predicting a positive clinical response.[20] Translational approaches are especially critical in adolescent research; given ongoing neurodevelopment, neural abnormalities and their malleability to treatment may be different in adolescents than adults. Severe depression is associated with impaired neuroplasticity.[21] Repetitive stimulation of synapses promotes growth of dendritic spines [22] and enhances neuronal excitability; these changes promote brain plasticity and recovery offunction.[15,23] The motor threshold (MT; the stimulus intensity required to achieve a reliable motor evoked potential [MEP]) and the MEP amplitude (MEPa) are measures of cortical excitability.[24] Recent developmental research using rTMS has shown that depressed youth have greater MTs than healthy youth, and that among depressed youth, MT decreases with age.[25] This emphasizes the opportunity to explore whether rTMS might reverse neuroplasticity/excitability

abnormalities in depressed youth, and the importance of studying adolescents separately from adults. Neuroimaging is another promising way to test the effects of rTMS on brain plasticity. Research has found that rTMS leads to increased regional cerebral blood flow in the DLPFC, anterior cingulate cortex, and limbic structures (e.g. amygdala).[26–28] Functional neuroimaging can measure resting state functional connectivity (RSFC); impaired RSFC within default mode and fronto-limbic networks have been found in depression.[29–32] rTMS can manipulate RSFC and potentially could restore abnormalities in depression.[33] Previous work examining RSFC before and after rTMS in adults with depression has shown that rTMS normalized abnormalities in the default mode network.[34] No imaging studies have been conducted examining how rTMS affects neural networks in adolescents with TRD. To advance current understanding of how rTMS impacts neuroplasticity, whether these changes are a key ingredient for the efficacy of rTMS, and whether these markers can predict treatment response, the current study will measure RSFC within neural networks, MT and MEPa before and after deep rTMS treatment in adolescents with TRD.

3. Investigational plan

3.1 Name of investigational device:

Brainsway Deep Transcranial Magnetic Stimulation (TMS) Machine

3.2 Intended use of the investigational device:

The Brainsway TMS machine will be used to provide repeated TMS (rTMS) as a novel treatment for adolescent treatment-resistant depression.

3.3 Objectives of the clinical investigation:

3.3.1 Primary objective.

To measure the feasibility, tolerability, safety and efficacy of a 30 session course of rTMS in adolescents with Treatment Resistant Depression (TRD).

3.3.2 Secondary objective(s).

a. To establish the optimal dose (energy of stimulation, measured by percentage of motor threshold [MT]) that balances safety and efficacy for adolescents with depression.

b. To examine whether changes in neuroplasticity promote successful rTMS treatment in adolescents with TRD.

c. To identify potential biomarkers for predicting a positive treatment response to deep rTMS that will be pursued in future research.

3.4 Title of clinical protocol:

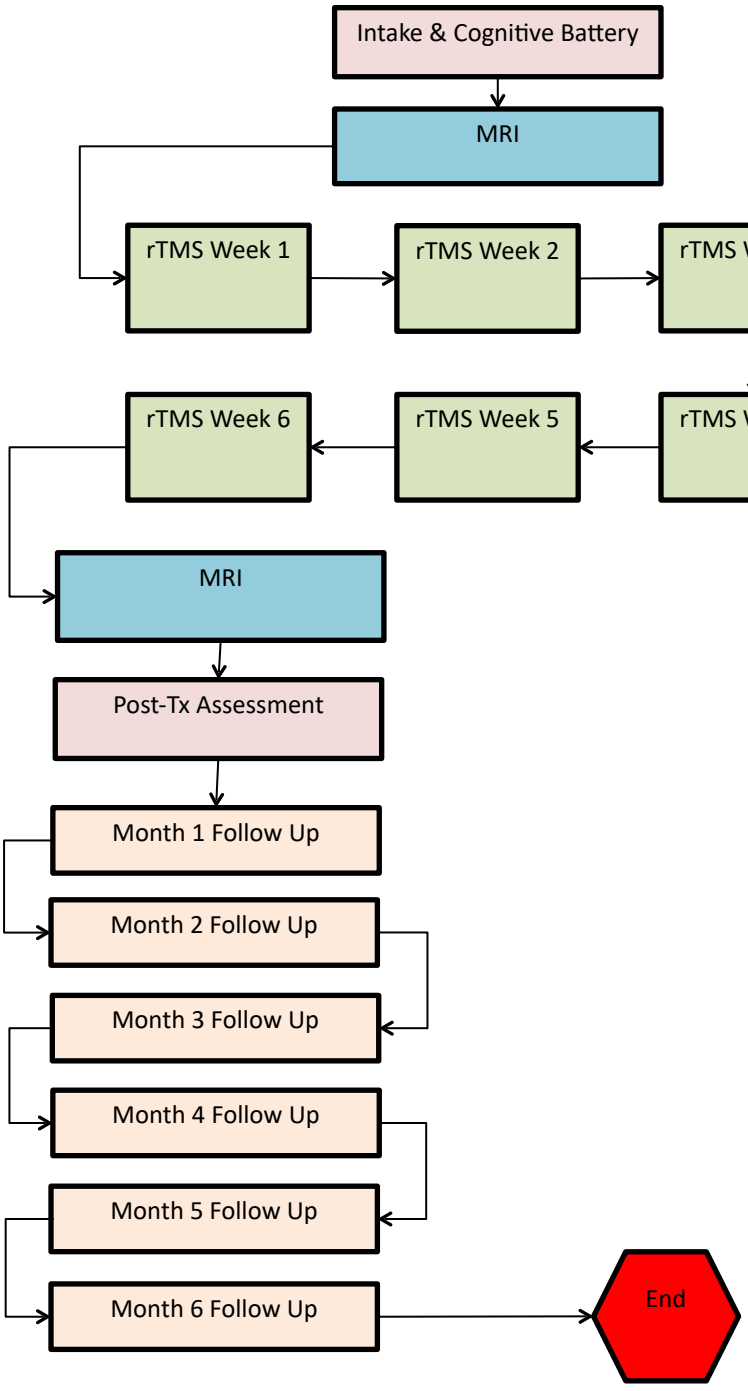
Repetitive Transcranial Magnetic Stimulation for Adolescent Depression: Efficacy, Predictive Biomarkers, and Mechanisms

3.5 Study design:

3.5.1 General study design.

1. This study will be an open-label 6-week (30 session) trial of active repetitive transcranial magnetic stimulation (rTMS) using a fixed frequency (10 Hz) and target stimulation intensity of 120% of MT. Some may receive a lower intensity as tolerated. If 2 participants experience a major safety event at 120% of MT, we will decrease the stimulation intensity to 100% of MT and complete the remainder of the subjects at that energy level.

3.5.2 Study design schematic.



3.6 Subject selection:

3.6.1 General characteristics of the proposed subject population(s).

Male and female adolescents aged 12-18 years old with a diagnosis of Major Depressive Disorder and who are currently in a depressive episode that has lasted at least 4 weeks who are resistant to antidepressant treatment as clinically defined by the study physician using the Antidepressant Treatment Record (ATR).

3.6.2 Anticipated number of research subjects.

The goal is to run a total of 30 participants through the protocol. In order to ensure that we enroll a sufficient number of adolescents with depression that will meet criteria for the study, we estimate that up to 60 participants will need to be consented into the study for initial psychiatric screening.

3.6.3 Inclusion/Exclusion criteria.

Inclusion Criteria	Determinant
Aged 12-18 years old	Phone screen, medical records (if available)
Diagnosis of Major Depressive Disorder	K-SADS, medical records (if available)
Experiencing a current MDD episode with a duration of ≥ 4 weeks	KSADS, medical records (if available)
A Children's Depression Rating Scale-Revised (CDRS-R) score of >40	CDRS-R
Resistance to treatment, defined by failure to respond adequately to at least one antidepressant treatment*	Antidepressant Treatment Record (ATR), patient/parent interview, discussion with treating physician (when possible), medical record (if
Female participants who are sexually active during the course of the study must use a form of birth control for the duration of the study	Phone screen, medical records (if available), Pregnancy test

Exclusion Criteria	Determinant
Any subject with a clinically defined neurological disorder or insult including, but not limited to, a condition likely to increase the risk of seizure; such as, space occupying brain lesion; any history of seizure; history of cerebrovascular accident; transient ischemic attack within two years; cerebral aneurysm; dementia; brain surgery; history of stroke	Phone screen, self-report, medical records (if available), CMRR safety screening form, TASS
Any subject with an increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure or history of significant head trauma with loss of consciousness for ≥ 5 minutes	Phone screen, self-report, medical records (if available), CMRR safety screening form, TASS
Failure of the Transcranial Magnetic Stimulation Adult Safety Screening (TASS) questionnaire as indicated by a positive response without clinician explanation and approval	TASS
Subjects with cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute unstable cardiac diseases	Phone screen, CMRR safety screening form, TASS
Subjects with conductive, ferromagnetic, or other magnetic-sensitive metals implanted in the head within 30 cm of the treatment coil excluding the mouth that cannot safely be removed should be excluded. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes	Phone screen, CMRR safety screening form, TASS
Subjects with active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators	Phone screen, CMRR safety screening form, TASS
Inability to locate and quantify a motor threshold as defined in the protocol	Initial rTMS visit
History of treatment with ECT or TMS therapy for any disorders	Phone Screen, ATR, medical records (if available)

Participation in any investigational drug trial within 4 weeks of the baseline visit	Phone Screen, ATR
Pregnancy	Urine pregnancy test (MRI appointment)
IQ < 80	WASI
Clinically significant laboratory abnormality or medical condition, that in the opinion of the investigator would hinder the subject in completing the procedures required by the study	Phone screen, medical records (if available)
Currently actively suicidal with intent and plan.	Phone screen, K-SADS, medical records (if available), BDI-II, C-SSRS, PHQ-9
Unstable psychotherapy (therapy must be for at least 3 months prior to entry into the study, with no anticipation of change in the frequency or treatment focus of the therapeutic sessions over the duration of the study)	Phone screen
A diagnosis of current substance use disorder (within the past 12 months), Schizophrenia, Bipolar Disorder, or Autism	Phone screen, K-SADS, medical records (if available)
Refusal to cooperate with study procedures	Consent appointment
Recent change (i.e., new medication or a dose increase) in dose of antidepressant medication (within 6 weeks prior to initial evaluation). This includes all antidepressants and any adjunctive psychotropic medications that are being used to address problems related to mood or anxiety (e.g. antipsychotic medications, mood stabilizers). **	Phone screen, ATR, medical records (if available), self-report, K-SADS
Current treatment with Bupropion at a dose greater than 150mg per day.	Phone screen, medical records (if available)
Current treatment with a stimulant medication as an adjunct medication for depression.***	Phone screen, medical records (if available)
Current treatment with a stimulant medication.***	Phone screen, medical records (if available), K-SADS

* Although we will use the ATR to record information regarding the duration and dose of each past or current medication trial, we will not use the ATR to define inclusion criteria. Rather, inclusion criteria will be defined as a failed trial to an antidepressant based on the impressions of the patient, parent/guardian and (when possible) treating clinician.

** If there has been a recent discontinuation or decrease in antidepressant dosage of a medication we will require varying lapses of time before study entry depending on medication type as follows: Antidepressant medications = 4 weeks, mood stabilizers (e.g. Lithium, Valproate) = 2 weeks, Antipsychotic medications = 2 weeks, Stimulant medications = 1 week

***If participants are being treated with stimulant medications for ADHD or as an adjunct strategy for their depression, we will require them to discontinue the stimulant prior to starting the study treatment and wait 1 week before they begin the study as listed above.

3.7 Study procedures:

3.7.1 Recruitment.

1. We will send letters and study brochures to local clinicians who treat adolescent depression.

2. We will screen electronic medical records of adolescents with a diagnosis of depression who are seen in the clinics and hospital services of the University of Minnesota, Medical Center and Masonic Children's Hospital. When potential cases are identified through screening, we will contact the treatment team to discuss whether the patient might be suitable for consideration for the study, and if so, we will ask the treatment team to request permission from the family to have the research team contact the family to explain the study. The outpatient Psychiatry Clinic in the Department of Psychiatry at the University of Minnesota provides new patients the opportunity to indicate whether they are interested in being contacted to hear about research studies or whether they prefer to not be contacted. Access to this contact information is managed by the Department of Psychiatry Research Recruitment Specialist. The Research Recruitment Specialist describes research opportunities to patients and provides the contact information of interested patients to departmental researchers conducting studies for which they might be eligible. We will receive this contact information to recruit participants for this study. We will

only contact patients who have indicated an interest in hearing about research.We will post flyers and advertisements in local community outlets about our study.

3. Research staff will utilize social media accounts such as (Facebook, Twitter, Instagram, independent website, etc.) to create an informative space about research opportunities and information about depression, self-harm and mental health for adolescents and young adults. Social media accounts for this research lab (RAD Lab) will be used for this study as well as accounts for the University of Minnesota Department of Psychiatry managed by the Research Recruitment Specialist working on behalf of research staff for recruitment. A coordinating website radlab.umn.edu will be used to describe participation information, including inclusion and exclusion criteria and amount of time to complete study. This information will also be listed on the UMN Department of Psychiatry website ("z.umn.edu/findastudy"). The website and media pages will provide study team contact information and IRB approval number. Media sites will be compliant with HIPAA: no identifying information will be collected and potential participants will be advised to contact the research team directly via phone or email for additional information about this study. The lab will include the following disclosure: "Disclaimer: The information on this site is not intended or implied to be a substitute for professional medical advice, diagnosis or treatment. All content, including text, graphics, images and information, contained on or available through this website, is for general information purposes only. Please contact your physician to form a plan that addresses you or your child's specific needs" wherever space is allotted.
4. Research staff, in coordination with the Research Recruitment Specialist, will create community engagement events for the purpose of education and awareness around adolescent depression, self-harm, mental health and the accompanied cultural stigma of seeking support. These events would focus on the needs of the community, awareness education, providing resources of support and mentioning this and other current research studies. All materials related to specific study recruitment would be submitted for approval.

3.7.2 Screening, consent and diagnostic procedures.

(a) The parent/guardian of each participant will first complete an initial, brief telephone interview with a research team member. The study will be briefly explained to the parent/guardian, and will ask a set of questions about the child's medical history. This

will serve to select participants likely to meet inclusionary criteria and to screen out participants who meet exclusionary criteria. Families that are interested in pursuing the study and who pass the screen will be scheduled for a diagnostic interview.

(b) The consent process will take place in the Ambulatory Research Center at the University of Minnesota. Consent and assent may also be obtained remotely using telecommunication (e.g., phone, Zoom). One of the members of the research staff will review the study procedures, risks and benefits as described in the consent form with the parent/guardian and in the assent form with the adolescent. The families will be given time to read the materials and ask any questions they have about the study. The research staff member will pose a set of questions to the parent/guardian and the adolescent to ensure that they fully understand the procedures, risks, and voluntary nature of the study. We will attempt to obtain consent from both parents except where it is not possible (e.g. death of a parent, parent does not have custody) or it is prohibitive to do so (e.g. parent lives in another state, parent is unavailable during reasonable business hours).
For remote consent procedures, we will either use REDCap, email (using encrypted email by including [encrypt] in the subject line), or mail the ICF to the participant or parent/ guardian. We will take special precautions to protect confidentiality (e.g. verify with the participant that the mailing address or email is correct and it is acceptable to send the consent in this way). The person consenting the participant or parent/guardian will have the same consent discussion remotely [e.g., over phone, zoom] that they would have had in-person (including asking questions to gauge comprehension and answering the participant's or parent/guardian's questions). The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be affected by their decision to participate in this study. If the participant or parent/guardian consents, they will complete and sign the ICF (in all appropriate sections) using REDCap email (using encrypted email by including [encrypt] in the subject line) a scanned PDF, fax, or mail the signed and dated ICF to the research team. A pre-paid, self-addressed envelope will be provided to the participant or parent/guardian if they choose to mail the signed ICF. Once the ICF (signed & dated by the participant or LAR) is received by the research team, the study team member who explained the study will sign the appropriate signature line with the current date. They will then send a copy of the fully executed ICF back to the participant. They will document the consent process in a separate note to file/ progress note. Study procedures will not begin until all aspects

of the remote consent process are complete. A copy of the ICF will not be included in the participant's Electronic Health Record.

(c) Directly after the consent process, families that have agreed to participate in the study will then participate in a comprehensive diagnostic assessment.

Clinician-administered measures: Separate diagnostic interviews with parent/guardian and adolescent will be conducted using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL). A member of the research staff will complete the Antidepressant Treatment Record (ATR), Clinical Global Impressions Scale (CGI), and the Children's Depression Rating Scale Revised (CDRS-R) with parent/guardian. A different member of the research team will complete the Children's Depression Rating Scale Revised (CDRS-R), Montgomery-Asberg Depression Scale (MADRS), Columbia Suicide Severity Rating Scale (C-SSRS), the Young Mania Rating Scale (YMRS), and the Edinburgh Handedness Scale with participant. These will be collected data using REDCap, a HIPAA-compliant data collection platforms.

Self-report clinical measures: Participants will also be asked to completed a number of self-report measures including the Beck Depression Inventory (BDI-II), Inventory of Depression and Anxiety Symptoms (IDAS), Temporal Experience of Pleasure Scale (TEPS), Snaith-Hamilton Pleasure Scale (SHAPS), State-Trait Anxiety Inventory (STAI) and the Tanner Pubertal Staging Questionnaire.

Neurocognitive measures: We will have the participant complete the Weschler Abbreviated Scale of Intelligence (WASI), two subtest version to obtain an accurate estimate of intelligence quotient (IQ) as well as a cognitive battery including the Attention Network Task (ANT), Dimensional Change Card Sort Task (DCCS), California Verbal Learning Test (CVLT-II), and the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test.

(d) After the diagnostic assessment is complete, a consensus meeting takes place among the research team to integrate the combined information from parent/guardian and adolescent KSADS interviews, rating scales and medical records (if available), to confirm the DSM-5 psychiatric diagnoses. If participants meet the above inclusion criteria and do not have any of the exclusion criteria, they will be invited to participate in the remaining portions of the study.

3.7.3 Pre- and Post rTMS Treatment Measurements of Neuroplasticity

MRI Procedures.

Prior to the MRI and beginning of TMS treatments, parents will be asked to complete safety screening forms to verify that their child is safe to undergo those procedures. The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publically available on the CMRR website (CMRR Policies / Procedures).If at any time it is discovered that a participant meets exclusion criteria, they will not be allowed to participate further in the study.

Scanning will take place at the Center for Magnetic Resonance Research (CMRR) on a 3T Siemens Prisma scanner at baseline (after the clinical assessment, before the first treatment) and after the last rTMS treatment. Participants will complete MRI safety forms and provide a urine sample to rule out substance use (all participants) and pregnancy (females only).

A high-resolution T1 image will be collected (voxel size=1mm isotropic; TR=2530ms; TE=3.65ms, T1=1100ms, flip angle=7°, 5 minutes).

Functional data will be acquired using the Human Connectome Project (HCP)38 multiband echo planar imaging sequence (whole brain T2*-weighted functional volumes, 72 contiguous slices; TR=720ms; TE=34.2ms; flip angle=55o, FOV=212mm; voxel size=2mm isotropic; matrix=106x106; multiband factor=8; 12 minutes) during rest with eyes open while viewing a fixation cross.

Participants will be asked to complete a task fMRI in which they are presented with a series of visual stimuli, (human faces of varying emotion expressions with positive, negative or neutral words printed over the faces). During the task, participants will be asked to decide whether the words printed over the faces are positive or negative regardless of the emotion of the face shown. Each subject will complete four distinct blocks of the task.

3.7.4 Study treatment procedures.

All study visits regarding TMS will take place in the Park Plaza Building, 5775 Wayzata Boulevard, St. Louis Park. The Brainsway

rTMS machine was FDA approved in 2008 as a treatment for depression in adults. It has not been FDA approved for use with children and adolescents at this time.

3.7.4.1. Allocation to treatment:

All participants will receive active rTMS. The target stimulation intensity for all subjects will be 120% of MT, but some may receive a lower intensity as tolerated. There is no longer a sham phase to this protocol. If 2 participants experience a major safety event at 120% of MT, we will decrease the stimulation intensity to 100% of MT and complete the remainder of the subjects at that energy level.

3.7.4.2. Initial Visit:
Side Effects Baseline Assessment. In the first treatment visit research staff will complete the Side Effects Form before treatment, in order to obtain a baseline assessment of pre-TMS treatment symptoms.

Motor Mapping and Treatment Tolerance. In the first visit, the study physician will fit the cap, determine the ideal location for stimulation, and measure motor threshold (MT) (the lowest energy intensity where a muscle twitch can be observed, or a depolarization measured by EMG, in the right abductor pollicus brevis, when the device is placed over the M1 region of the left motor cortex). Beginning at 80% to 100% of MT, we will gradually titrate up the intensity to 120% depending on participant tolerance, increasing no faster than 10% of MT daily (as applicable). This is done until the participant is able to tolerate 120% of MT for the duration of their 30 treatment sessions. If the participant has not been able to titrate up to 120% of MT after 2 weeks, they will complete the study treatment visits at the most tolerable % of MT, as clinically determined by on-site treating Psychiatrist. The 30 treatment sessions will begin at this first visit and include all subsequent titration visits even if participant is not able to tolerate 120% of MT.

3.7.4.3. Study Treatment:

Adolescents will receive 6 weeks of active rTMS, targeting mainly the left DLPFC for 20 minutes/day, 5 days/week administered by a trained technician. Active treatment will be 55 trains of 10 Hz, train duration 3.6 seconds, stimulation intensity and titration as described above, inter-train interval 20 seconds, 1980 pulses/ session.

Participants will be asked to complete the Patient Health Questionnaire (PHQ-9) and have their vitals taken daily before each rTMS session.

A member of the research staff will meet weekly with patients and parent/guardians to complete the Children's Depression Rate Scale Revised (CDRS-R). Participants will meet with study staff who will adminsiter the Young Mania Rating Scale (YMRS), Clinical Global Impressions Scale (CGI), Montgomery-Asberg Depression Rating Scale (MADRS), and Columbia Suicide Severity Rating Scale – Since Last Visit (C-SSRS SLV) . The research staff will also monitor treatment tolerance using the Side Effects Form for Children and Adolescents. Adolescents will also complete the self-report Beck Depression Inventory (BDI-II), State-Trait Anxiety Inventory (STAI), the Temporal Experience of Pleasure Scale (TEPS), and the Snaith-Hamilton Pleasure Scale (SHAPS) weekly. At week 6, the participants will be asked to repeat the ANT, DCCS, California Verbal Learning Test (CVLT-II), and the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test. The TMS operator will measure MT and MEPa weekly. In addition, the MT and MEPa will be repeated as deemed clinically necessary by research staff based on patient symptoms and side effects.

After the completion of treatment, all participants will undergo a final assessment during which they and their parents will be asked to meet with evaluators again to complete the CDRS-R. Participants will also be asked to complete the BDI-II, MADRS, CGI, C-SSRS, STAI, TEPS, SHAPS, and IDAS.

All measures with the exception of the DKEFS, Ant, DCCS and CVLT-II will be collected via REDCap, a HIPAA-compliant data collection platform.

3.7.4.4 Breaking the blind:

None of the participants in this study will be blinded to their study conditions.

3.7.4.5 Treatment adherence/Study compliance:

Participants will not need to be monitored for non-compliance of device procedures as their treatments will be administered by a trained technician. However, if a participant neglects to attend treatment sessions, they will be excluded from the study.

3.7.5 Follow-up procedures.

3.7.5.1 Procedures to assess efficacy**:**

During the course of treatment, a member of research staff will meet with study participants on a weekly basis to measure MT and MEPa and to complete the Children's Depression Rating Scale – Revised (CDRS-R) with the participant. The participant will also complete the Beck Depression Inventory-II (BDI-II) on a weekly basis. These depression scales will be compared throughout the course of the study to look for improvement.

After treatment has been completed, participants will be re-assessed to determine their level of depressive symptoms post-treatment. Participants whose CDRS-R scores have decreased by at least 50% will be considered treatment responders.

All participants will be asked to complete 6 monthly follow-up appointments by in-person or video conferencing interview to assess the length of response to treatment and monitor the effects of treatment long term.

Remote Conduct of Study Procedures

(a) Study staff will collect data using HIPAA-compliant data collection platforms (e.g., REDCap, Zoom) as necessary during the period of heightened public health concern due to COVID-19.

(b) The above practices are in accordance with the Office of the Vice President for Research's documents *Human Research Checklist: Preparing for Impact of COVID-19* and *Frequently Asked Questions: COVID-19 and Human Research* released by the UMN Human Research Protection Program at the University of Minnesota, Twin Cities on March 10, 2020 and March 11, 2020 (respectively).

3.7.5.2 Procedures to assess safety:

During the course of treatment, a member of the research staff will meet with study participants on a weekly basis to monitor treatment tolerance using the Side Effects Form for Children and Adolescents. *During the course of treatment, MT will be monitored to make sure it doesn't decrease by more than 10% from week to week. MT will also be assessed and adjusted based on clinical presentation of the participant (i.e. if participant experiences side effects potentially related to MT needing to change before the scheduled weekly adjustment). A cognitive battery will be used at baseline and week 6 to assure there are not any significant changes in cognitive function due to treatment. We will also administer the Young Mania Rating Scale (YMRS) on a weekly basis to assure that participants are not experiencing treatment-induced mania. The Clinical Global*

Impressions scale (CGI) will be given on a weekly basis. If the participant scores a 6 or 7 on the CGI, it will prompt a conversation between the PI, the treating TMS physician, the participant and the parent/guardian about whether or not they should continue in the study. The conversation and decision will be documented.

Suicide risk will be monitored at each visit using the Columbia Suicide Severity Rating Scale (C-SSRS). If the participant is deemed to be acutely suicidal, he or she will be referred for appropriate emergency treatment and will exit the study.

3.7.6 Schedule of activities (Study Table).

	Intake	MRI 1	rTMS Week 1	rTMS Week 2	rTMS Week 3	rTMS Week 4	rTMS Week 5	rTMS Week 6	MRI 2	Final Assessment	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
Consent	*X*															
KSAD-S	*X*															
CDRS-R	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*
BDI-II	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
C-SSRS (LV or	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*
TEPS	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*
SHAPS	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*
IDAS	*X*									*X*	*X*	*X*	*X*	*X*	*X*	*X*
Side Effects Form			*X*	*X*	*X*	*X*	*X*	*X*								
Safety Screen		*X*	*X*						*X*							
UTox		*X*							*X*							
Pregnancy Test		*X*							*X*							
MRI		*X*							*X*							
rTMS			*X*	*X*	*X*	*X*	*X*	*X*								
MT			*X*	*X*	*X*	*X*	*X*	*X*								
MEPa			*X*	*X*	*X*	*X*	*X*	*X*								
YMRS	*X*		*X*	*X*	*X*	*X*	*X*	*X*								
ANT	*X*							*X*								
D-KEFS Trail	*X*							*X*								
CVLT-II	*X*							*X*								
WASI	*X*															
ATR	*X*															

	Intake	MRI 1	rTMS Week 1	rTMS Week 2	rTMS Week 3	rTMS Week 4	rTMS Week 5	rTMS Week 6	MRI 2	Final Assessment	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
Edinburgh	*X*															
Tanner	*X*															
PHQ-9			*X*	*X*	*X*	*X*	*X*	*X*								
STAI	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*						
MADRS	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*						
CGI	*X*		*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*
DCCS	*X*							*X*								

3.8 Study outcome evaluations:

3.8.1 Study endpoints.

Primary outcome measure: CDRS-R.

Secondary outcome measures:
BDI-II, C-SSRS, TEPS, SHAPS, IDAS, MADRS, CGI, STAI

Endpoint for all participants is after the completion of the 6-month follow-up appointment.

3.8.2 Sample size determination.

The purpose of this study is to obtain pilot data upon which to base a subsequent pivotal study of rTMS for adolescents with TRD. We have chosen a total sample size of 30.

3.8.3 Outcome data and data analysis.

3.8.3.1 rTMS intensity safety analysis

The design of this study will allow us to collect data on which levels of stimulation intensity are safe to use with adolescent participants.

3.8.3.2 rTMS effectiveness data analysis

Repeated measures ANOVAs will examine the effects of rTMS at varying levels of stimulation intensities (80%, 100% and 120% of MT) on weekly CDRS-R scores and on measures of neuroplasticity change (pre- vs. post-treatment RSFC, MET, and MEPa scores). Separate analyses of the pre- vs post-treatment CDRS-R scores will include group, neuroplasticity change measures, and interaction terms to identify whether change in neuroplasticity moderates reduction in depression symptoms. Parallel analyses will use logic regression with binary responder vs. non-responder outcomes. To identify potentially predictive biomarkers of responsiveness to rTMS, logistic regression of responder vs. non-responder on measures of baseline measures of neuroplasticity will be used.

3.8.3.3 Neuroimaging data analysis

We will optimize components from the HCP minimum processing pipeline to fit our imaging protocols and will include gradient non-linearity distortion corrections, distortion correction caused by magnetic field inhomogeneity, co-registration of functional and anatomical images, non-linear registration to MNI template brain, intensity bias corrections, highpass filtering, re-sampling of the data onto the cortical mesh (surface analyses), and denoising of

the data using ICA-fix.[40] Network Analysis. We will quantify RSFC within fronto-limbic and default mode networks as described in our prior work.

4. Risk analysis

4.1 Anticipated risks:

4.1.1 Screening Visit

Our clinical assessment of all adolescents and parents of children enrolled in the study involves asking questions about feelings, past experiences, and family history. Some of these topics may cause the subjects and/or their parents discomfort or distress. Participants are encouraged to share only what they feel comfortable with and will not be induced to discuss anything that makes them too uncomfortable.

4.1.2. Repetitive Deep Transcranial Magnetic Stimulation (rTMS)

The device to be used in this study is a Brainsway Repetitive Deep Transcranial Magnetic Stimulation (rTMS) machine. rTMS is considered to be a safe brain stimulation technique that rarely results in adverse events. However, there is a risk that rTMS could induce a seizure in the participant. Because of standards set for rTMS, the risk of seizure has been very well contained. Our treatment parameters are well within these safety guidelines. We will ask subjects if they have any medical conditions and if they are taking any medications. Important medical information such as pro-epileptic medications and no history of seizure will be collected to screen out those at risk for a rTMS-induced seizure. Safe practices will be further ensured by establishing the location for testing and treatment within the University of Minnesota's Ambulatory Research Center (ARC) which is located one floor above the Emergency Room of the University of Minnesota Medical Center (UMMC) Riverside hospital or at the MINCEP Epilepsy Clinic in St. Louis Park. Research team members that will be administering rTMS will be trained in CPR and in seizure first aid. In the event that a participant has a seizure in the ARC, research team members will provide initial support and call 888, which will prompt hospital staff to come to assist the participant. In the event that a research participant has a seizure at the MINCEP Clinic, the staff if equipped to provide treatment.

One of the risks associated with rTMS is treatment-induced mania. A member of the research staff will perform the Young Mania Rating Scale (YMRS) with the participant each week to determine if the participant is experiencing symptoms of mania.

Other mild adverse effects include fainting, headache, dental pain, and other changes in memory, mood, and hearing. The overall occurrence of mild adverse events is 5% in sham and real rTMS

combined. If headaches or dental pain occur, the participant will be given Acetaminophen.

In extreme situations, for subjects reporting pain or discomfort that is severe or intolerable, topical application of lidocaine at the treatment site has been found to be useful and may be used, at the discretion of the site PI, for this study. Additionally, study personnel may decrease the "intensity" of the treatment strength to 80% of MT as necessary. It is common that the scalp discomfort abates following the first 2-3 treatments. Titration to maximum treatment power will occur as tolerated by each subject. Although if titration to the assigned intensity has not occurred after 2 weeks, the participant will be excluded from the study. Any report of scalp burning sensation by a subject will result in discontinuation of treatment for the day. Treatment would be offered the following day or as tolerated within the study timeframe

rTMS may interfere with implanted devices. rTMS is not appropriate for persons with medical devices such as deep brain stimulators, pace-makers, and medication pumps. Participants will be screened for previous surgeries that might include metal, indwelling medical devices, etc. Participants with devices, etc. will not be allowed to participate.

It can be very loud while receiving rTMS. This can be uncomfortable and may affect the participant's hearing. Participants will be asked to wear ear plugs which will significantly reduce the amount of noise.

4.1.3. MRI scanning

The device to be used in the study is a 3 Tesla Seimens Prisma MRI machine.

The magnet in the scanner may cause electronic devices like watches to malfunction, and some metal objects can be pulled into the scanner. Participants will be screened prior to the scan to make sure they have nothing in their body which could be magnetic or affected by the magnetic field of the scanner. Participants will be asked to change into scrubs to ensure they have no metal on their person.

It may be uncomfortable lying still in the scanner for the amount of time required. The participant may experience some stiffness and soreness in the muscles from being still. To make participants as comfortable as possible, we will provide soft pads to help support the next, back, and legs.

The scanner itself makes a lot of noise while it is running. This can be uncomfortable and may affect the participant's hearing. Participants will be asked to wear ear plugs which will significantly reduce the amount of noise. Participants will also be wearing headphones in addition to the earplugs to allow them to hear the investigators and listen to music.

Some people may become uncomfortable in the scanner because they are not comfortable being in enclosed spaces. We will screen for claustrophobia before we bring the participant to the scan center. They will have the option of using a mock scanner prior to going into the scanner to assess their level of comfort. They will not be required to participate in the scan or continue the scan if they are uncomfortable.

There is a chance we may discover that the participant is pregnant. We may also obtain a false positive with the urine toxicology screen or pregnancy test. If we discover a participant is pregnant, we will let them know. We will also inform them of the risk of obtaining a false positive and encourage them to follow up with their primary care physician. Although there are no known risks associated with scanning pregnant women, we will not scan someone who is pregnant. We will not inform the participant’s parent of the results unless we feel the pregnancy would cause serious problems for the participant.

There is a chance we might find something abnormal when we look at the images of the participant's brain. We will send all images to a trained radiologist after the scan so they can be assessed for abnormalities. These images will not have any identifying information about the patient. If the radiologist recommendation is to further investigate the unusual results of the pictures, the investigator will contact the participant.

4.1.4. Text Message Risks

Participants will be able to opt in to communicating with study staff via text message to arrange their appointments and receive study instructions. There are risks associated with communication via text message. Risks of sending or receiving text messages include, but are not limited to:

- Others can intercept messages
- Text messages may be viewed by University of Minnesota staff depending on the nature and timing of said messages, and may be monitored by the University to ensure appropriate use.

If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The cell-phone provider may also have the right to save and read text messages.

4.2 Adverse event recording/reporting

4.2.1 Adverse event definitions.

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was

not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.2.2 Eliciting adverse effect information.

Clinical study subjects will be routinely questioned about adverse effects at study visits.

4.2.3 Recording and assessment of adverse effects.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

4.2.3.1 *Abnormal test findings*:

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.

- The test finding is considered an adverse effect by the investigator-sponsor.

4.2.3.2 *Causality and severity assessment*:

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

4.2.4 Reporting of adverse effects to the FDA.

The investigator-sponsor will submit a completed Form FDA 3500 A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an *unanticipated adverse device effect. A* copy of this completed form will be provided to all participating sub-investigators.

The completed Form FDA 3500 Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an *unanticipated adverse device effect* does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed Form FDA 3500 A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted Form FDA 3500 A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the

significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed Form FDA 3500 A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

4.2.5 Reporting of adverse effects to the responsible IRB.

In accordance with applicable policies of the University of Minnesota Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s)*; 2) *a serious adverse effect*; and 3) an *unexpected adverse effect*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) *associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

4.3 Withdrawal of subjects due to adverse effects:

Subjects who experience severe adverse events including a seizure, treatment-induced mania, or other unanticipated problem where the study physician feels it would be unsafe for the patient to continue, will be immediately withdrawn from the study. In the case of other serious adverse events, the study physician and the patient/family will decide whether it would be safe and prudent to have the subject continue in the study based on the situation. Subjects who experience mild to moderate adverse events will be allowed to discontinue if they choose.

Subjects withdrawn from study participation due to an adverse effect will not be replaced as we have included more people than necessary in our original sample size for situations such as subject withdrawal or bad MRI data.

4.4 Stopping Rules

In certain cases, participants will be withdrawn from the study for their safety. These cases include:

- A seizure,
- Treatment induced mania as indicated by a YMRS score of ≥14,
- A suicide attempt or acutely suicidal with plan of intent.
- The MT decreases by more than 10% from one week to the next, or decreases to where it is 70% or lower than the baseline MT.
- Excessive motor activation develops (movements in upper or lower extremities) for more than 3 treatments at the assigned % of motor threshold for that participant.
- The participant cannot tolerate treatment at the assigned % of motor threshold for that participant.
- The participant's depression has significantly worsened (received a 6 or 7 on the CGI), and either the P.I., the study physician, the participant, the parent felt that it would be in the patient's best interest to stop the study.
- TMS technologist is unable to locate and quantify a motor threshold.

5. Description of the device

We will be using a Brainsway Deep Transcranial Magnetic Stimulation device for this study. This device utilizes an H-coil within a helmet to deliver stimulation to participants.

The department of Psychiatry has already purchased a BrainSway rTMS machine, which has been installed in the MINCEP Epilepsy Clinic in St. Louis Park. Periodically, the machine may be moved to the Ambulatory Research Center (ARC) during periods of transition at the MINCEP Clinic. Therefore the equipment and personnel will be ready for the project. The BrainSway company has provided assurance that we will be able to use the machine at no cost for the study participants

No changes to the investigational device during the course of the study are anticipated.

6. Monitoring procedures

Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of Minnesota's Clinical and Translational Science Institute (CTSI) monitoring staff.

The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

7. Manufacturing information

Brainsway, manufacturer of the Brainsway Deep TMS System, is certified by and operates according to the ISO Quality Management standards: ISO 1348: 2008 +AC: 2012

This ensures that Brainsway applies and maintains its Quality Management System according to strict guidelines. All departments within Brainsway, including Manufacturing, Processing, Packing, Storage and Installation are monitored in accordance with the ISO 1348: 2008 and all GMP Guidelines

Brainsway also has a Quality Assurance department which checks the various processes in place within standard work processes.

All information is stored and allows Brainsway to perform traceability of any given product.

8. Investigator information

The proposed research team has the combined expertise necessary to conduct the proposed innovative study testing deep rTMS in adolescents with TRD and measuring its associated brain mechanisms. Our team has a strong track record of collaborating that has led to important advances in identifying neurobiological indices of adolescent depression. All investigators involved in the proposed study are committed to (a) conducting the investigation in accordance with the investigational plan and FDA regulations; (b) supervising all testing of the device; and (c) ensuring that the requirements for obtaining informed consent are met.

Dr. Kathryn Cullen, the P.I., is a child and adolescent psychiatrist in the Department of Psychiatry who has been practicing and conducting research with depressed adolescents over the past eight years. She is P.I. on two NIH-sponsored grants using MRI technology to evaluate adolescent depression and self-injury. She is in the process of conducting a number of treatment trials, including a parallel study testing ketamine as a novel treatment for adolescents with TRD.

Dr. Bonnie Klimes-Dougan is a faculty member in the Psychology Department who has been conducting clinical evaluations and research on adolescent depression for the past 20 years and has been collaborating with Dr. Cullen on adolescent depression studies for eight years. She supervises a practicum for Ph.D. psychology students who will conduct clinical assessments of the adolescent participants and their parents under her supervision. She will also assist in providing "blind", unbiased post-treatment clinical assessment to determine treatment responsiveness.

Dr. Kelvin Lim is a psychiatrist and neuroimaging expert whose work has recently moved into using neuromodulation techniques to understand and treat mental illness. Dr. Lim served as a research mentor to Dr. Cullen for her NIH career development award, and they continue to work closely on several different projects.

Dr. Suma Jacob, M.D. is an associate professor of Child and Adolescent Psychiatry at the University of Minnesota who has significant experience in clinical trials in child and adolescent psychiatric disorders. Dr. Jacob has undergone TMS training through BrainSway.

Dr. Bryon Mueller is an MRI physicist land an expert in applying the proposed advanced technology to examine brain networks, and is an invaluable member of the team. He will develop and implement the proposed neuroimaging protocol and supervise the processing and imaging data analyses.

Dr. Lynn Eberly is an expert statistician from the Division of Biostatistics, School of Public Health. She serves as Dr. Cullen's statistics mentor on her

NIH K23 award and on her CTSI K to R award, and is a co-principal investigator with Dr. Cullen on a translational trial testing the impact of a novel medication on brain circuitry in adolescents with self-injury. Dr. Eberly's expertise in longitudinal statistical analysis incorporating clinical and imaging measures is necessary for the project's successful completion.

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9. IRB Information

Significant public scrutiny and media coverage have occurred over the past year regarding psychiatric investigational drug trials performed at the University of Minnesota, including the institutional review of such studies. As such, the University of Minnesota has decided to transfer review of all clinical trials taking place within the Department of Psychiatry to Quorum Review IRB.

Quorum Review IRB
1501 Fourth Avenue, Suite 800
Seattle, WA 98101
Phone: (877) 472-9883
(206) 448-4082
Fax: (206) 448-4193

For more information about the individuals who comprise the IRB review panels, please see the attached document.

10. Sales information

The device is not being sold or leased for purposes of the Study. The Device is Brainsway property, which is currently stationed at Research Institution's premises via a separate unrelated agreement. Pending signature of a CTA, Brainsway agrees for the device to be used for purposes of this Study.

11. Environmental impact statement

An environmental impact assessment or claim for categorical exclusion is no longer required per 21 CFR 25.34(g).

12. Labeling

Please refer to the FDA-approved Instructions for Use (IFU) for the system, attached hereto as **Exhibit A**. Caution: Use of the system in a manner not consistent with the IFU constitutes investigational use and may entail significantly increased risk.

13. Informed consent materials

Please see attached Consent, Assent, and HIPAA forms.

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