ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff, or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact: ancillaryreview@Fairview.org*	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☐ **Yes** ☒ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance on the next page.	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam, or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval.** **These groups each have their own application process.**
☒ **Yes** ☐ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu Contact:*	
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol. Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff. Contact: cdrifka@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff Contact: becca002@umn.edu*	

☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff Contact: kmmccorm@umn.edu*	**process but additional information from the study team may be required.**
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	**Protocol Title: Teen Brain Training (TBT)** **Grant: Neurofeedback and Neural Plasticity of Self-Processing and Affect Regulation Circuits in Suicide Attempting Participants**
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Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	NA
IND/IDE Holder	NA
Investigational Drug Services # (if applicable)	NA
Version Number/Date:	Version **4 / 10/27/2023**

Grant NIMH Number: 1R61MH122634
Grant Title: Neurofeedback and Neural Plasticity of Self-Processing and Affect Regulation Circuits in Suicide Attempting Participants

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	5/04/2022	• Removed specific names of staff involved in the study. • Allowed for use of Box for a repository for data and personal health information. • Email and Text Authorization can be signed during the screening process. • Added new numbers. • Removed old devices This is unrelated to changes in the consent documents that also took place.	YES (phone number + fields).
2	11/15/2022	• Payment of 4th visit will depend on the instances of rescheduling for Visit 1-Visit 3. • Allowed for use of 3rd party vendors and airplane ticket to provide transportation to participant • Consent for arranging transportation can be signed during the screening process and during the 1st visit. • Parking compensation can be provided via a parking voucher or up to $13 compensation.	YES (payment field and transportation field).
3.	06/21/2023	• Added RSES, DES-2, DSS, BPQ, CTS2, CALPAS, WAI, WAI-SR, ECR-R questionnaires to page 13 • Changed "youths" to "Participants" • Expand the population group to 17 y.o – 45 y.o with Borderline Personality Disorder	Yes
4	10/27/2023	• Expanded the inclusionary criteria to also include participants with 1) any suicide ideation history regardless of suicide attempt histories; 2) any suicide attempt history regardless of current or past suicide ideation severity; and 3) depressed participants with neither suicide ideation nor attempt history. • Spelling and grammar edits • added SCID-5-CV, SCID-5-PD, and MMPI-A-RF as screening tools for BPD groups • Clarified exclusionary criteria for 11-18 year-olds and 17-45 year-olds • Clarified the risk vs protective factors for participants with high suicide ideation as cumulative factors to determine exclusionary vs inclusionary.	Yes

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ABBREVIATIONS/DEFINITIONS

ACC: anterior cingulate cortex;

AMY, amygdala;
CTSI: Clinical Translational Science Institute
CRAS: clinical research associates
BHRRC: Behavioral Health Research Review Committee
DSMP: Data Safety and Monitoring Plan;
EBT; Emotional Testing Battery;
ESOM_Q, Emotion Self-Other Morph Query;
ESOM_NF, Emotional-Self-Other Morph Neurofeedback
ESOM-Pre, ESOM task presented before ESOM_NF task
ESOM-Post, ESOM task presented after ESOM_NF task
ER; Emotion Regulation Task;
FC; functional connectivity
IAT, Implicit Association Test;
IMM; Independent Medical Monitor;
MDD: Major Depressive Disorder;
mPFC, Medial Prefrontal Cortex;
mPFC FC; medial prefrontal cortex functional connectivity
NF, Neurofeedback;
QR; Quick Response Code
ROI, region of interest;
PTSD: Post Traumatic Stress Disorder;
Personal Health Information: PHI
UMN: University of Minnesota

1. Objectives

R61 Phase Specific Aims: Given the modest efficacy of current evidence-based treatments [1-7], novel, personalized interventions for adolescent suicide behaviors are needed. Repeated suicide attempts are predicted by abnormal self-processing and affect dysregulation [4,8-13]. Abnormal self-processing is neglect of positive self-relevant information and excessive focus on negative information. Self-processing (e.g., self-face recognition) is enabled by the dorsal anterior cingulate cortex (**dACC**) [14-16] and medial prefrontal cortex (**mPFC**) [40-4]. Those neural hubs enable awareness of salient stimuli [17] and affect regulation, which is modulation of emotions borne by neural hubs such as the **amygdala** [18]. Adolescence is a neuroplastic period for the circuits of affect regulation and self-processing [19,20]. It is unknown whether engaging those circuits using novel interventions could reduce suicide risks, e.g., suicide ideation. To begin to address this knowledge gap, in the R61 phase we will test the efficacy of neurofeedback training to engage the neurocircuitry of self-processing and emotion regulation (dACC, mPFC and amygdala) in 1st time suicide attempting Participants.

To establish target engagement, **in the R61 phase**, participants will be trained to increase the activity of one of two competing neural hubs ($\mathbf{N_{dACC}}$=20 or $\mathbf{N_{Right\text{-}Amygdala}}$=20). We will identify which circuits are better engaged during and after NF in time suicide attempting participants (11-18 years) with current suicide ideation as well as 17 – 45 y.o participants with symptoms of borderline personality disorder. Behavior and circuits of affect regulation and self-processing will be sampled before and after two NF training sessions.

The **R61 milestones for proceeding to the R33 phase are**:

Milestone 1: NF loci (dACC or amygdala) must show higher activity during ESF-NF and higher FC with mPFC after NF training during the ESOM or ER tasks with effect sizes of d ≥0.4.

Milestone 2: 20% of variance in psychological target's change (ETB, IAT) must be associated with amygdala or dACC to mPFC FC changes during the ESOM or ER tasks after NF.

If those milestones are met, during **the R33 phase**, 70 suicide attempting participants with pre-NF assessments will be randomized 1:1 to: NF or NF from a region that is not related to memory recall, labeled as "**Unrelated-NF**". Participants will be matched in sex, age, IQ, illness severity, suicide ideation, and abuse history if possible. Leveraging Bayesian methods to increase power, our aims and hypothesis (**H**) for the R33 phase are:

R33 Aim 1. Confirm target engagement in the NF versus the Unrelated-NF group.
H1.1: Right amygdala or dACC activity will be higher for active versus Unrelated-NF.
H1.2: Right amygdala or dACC – mPFC FC will be higher during self-processing and affect regulation tasks following active NF compared to Unrelated-NF training sessions.

R33 Aim 2. Test the relationship between neural and psychological targets' engagement and suicide ideation. H2.1: Lower affect dysregulation and abnormal self-processing behavior will follow active NF as compared to Unrelated-NF, mediated by amygdala or dACC to mPFC FC changes in self-processing and affect regulation tasks. H2.2: Higher amygdala or dACC to mPFC FC after NF will be associated with lower suicide ideation. H2.3: Affect dysregulation or abnormal self-processing behavioral changes will mediate the association between changes in FC and suicide ideation before versus after NF.

2. Background

Suicide is the 2nd leading cause of adolescent death in the U.S [21]. Yet it is increasingly acknowledged that current evidence-based interventions for illnesses linked to suicide ideation and attempts underperform across the lifespan [1-7,22].

3. Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

The primary outcome of the R61 stage will be the fMRI imaging results, behavioral tasks (IAT and EBT) and self-reported suicide ideation data. The DERS[23], RD[120] and the SPPA[24,25] will provide self-report measures of affect dysregulation and abnormal self-processing. **The primary outcomes of the R33 stage** are similar as above but now include the C-SSRS [98] and SIQ [29] to test changes in suicide ideation and attempts

Secondary Outcome(s): The secondary outcome measures are the new computerized KSADS-COMP based on the K-SADS-PL [26]; symptoms are measured dimensionally on a 4-point scale and scores and notes are entered on a tablet computer. The BDI[27] and CTQ [28] will yield additional dimensional depression and PTSD indexes. The C-SSRS [98] and SIQ [29] will confirm suicide ideation and attempts at baseline. The CDRS, Suicide Ideation Questionnaire, Children's Attributional Style Questionnaire (CASQ), Positive and Negative Affect Schedule (PANAS), and Responses to Depression (RD) Rumination Scale along other questionnaires will be administered during follow-up assessments after the last scanning.

4. Study Intervention(s)/Investigational Agent(s)

Description. Neurofeedback training is a modality of biofeedback. During neurofeedback training, a person that is inside the scanner can see the changing levels of activity of a selected brain region. Because regional neural activity is visually displayed to a person in the scanner, this enables voluntary modulation of neural activity in regions of interest, which can trigger corrective neuroplastic processes. We will deliver neurofeedback training using the **Emotional Self-Face Neurofeedback, ESF-NF paradigm** [30,31] comprised by four ~7.33 min NF training runs preceded by a 5 min baseline (ESF no NF), a 5 min practice run, and followed by a 5 min transfer run (ESF no NF) [32]**.** Training entails NF blocks paired to a self-happy face visual that signals the start of NF. There will be two control conditions to distract participants from contemplating positive memories and dampen affect regulation and self-processing networks. During one control condition participants will count backwards from 100 cued by an unfamiliar happy teen face with no NF (count backward = **CB**). During other control condition participants are presented with the cue "Rest" and are asked to relax and look at the screen (**Rest**). During **NF**, participants will attempt to increase neural activity displayed via a colored bar shifting up or down depending on values provided by MURFI2 software [33]. Green = Activity > baseline and red = Activity < baseline. We may adapt the feedback procedures to be more like a game, but the current description still conveys the visual feedback modality. The active NF loci will be the right amygdala or the dorsal ACC in the R61 phase. The active NF loci during the R33 phase will be the loci of higher engagement that best elicits functional improvements in the R61 phase. As in prior NF trials [34-36], participants select positive autobiographical memories that they recall during NF training. Dr. Quevedo has administered a short version of the proposed task to 53 Participants [30,31]. ROIs for the dACC, right amygdala or an unrelated site (e.g., the left intraparietal sulcus) will be localized from coordinates mapped to each participant's structural image. Dr. Quevedo has used this software and protocol with healthy and depressed participants [30,31]. The scanning room and specifically the scanner coils already include devices to present stimuli. It is part of the hardware. We may monitor heart rate and breathing using devices that are superficially attached to the participant's torso. These devices are also often used as part of scanning procedures of human participants.

4.1 Drug/Device Handling: NA

4.2 Biosafety: NA

4.3 Stem Cells: NA

4.4 Fetal Tissue: NA

5. Procedures Involved

Study Design: After securing a permission to contact from participants or parents, study personnel will screen suitability (See Phone Script) with parents or legal representatives over the phone before scheduling the first session. Participants will be assessed in person ~2 weeks before and after NF training (Day 1: first session) and ~1 month after the last NF training. The first session visit can occur at the department of psychiatry, at the impatient unit where the participant might still be interned, or in the same building where the patient unit is at (with permission of the leadership in the inpatient unit and provided that a secure confidential room is available).

Two to three weeks can pass between each visit. Responses from parents and clinicians might also be used for preliminary screening of participants and their families over the phone, to establish eligibility for in-person assessments. Table 1 provides the sequence of key events. **To confirm inclusion and enable brain-behavior analyses, disorders will be established by clinicians administering the new computerized KSADS-COMP or the K-SADS-PL [26] interview version lead by a trained staff member.** The BDI[27] and CTQ [28] will yield additional dimensional depression and PTSD indexes. The C-SSRS [98] and SIQ [29] will confirm suicide ideation and attempts at baseline. The DERS[23], RD[120] and the SPPA[24,25] will provide self-report measures of affect dysregulation and abnormal self-processing. Participants will also complete the IAT[38,39] a behavioral task of abnormal self-processing and the Emotional Testing Battery (ETB), which measures affect regulation and self-processing [40] outside the scanner. After concluding the 1-month follow-up participants that accept remaining in touch with the experimenters may be called for

another follow-up brief phone interview and/or to be invited to other studies. This optional follow-up involves administering a few previously approved questionnaires that will measure depressed mood, feelings, suicidal thoughts and/or suicidal feelings since they last participated. **Before and after the NF training participants will complete the following tasks or alternative tasks that measure the similar constructs of affect regulation and self-processing. The following tasks are exemplars of what the participant will experience.**

Emotional Self-Other Morph (ESOM) task [41,42]**.** Before and after NF training, participants will identify their own or another teen's face with happy, neutral, or sad expressions via button press in the scanner. Faces (N=150) are presented against a black background and drawn out of 21 possible composites (5% increments) that range from 0% self and 100% other or 100% self and 0% other. We have published that ACC and mPFC activity and ACC-right amygdala functional connectivity during self vs. other-face recognition distinguishes adolescent suicide attempters vs. both depressed and healthy participants [41,42]. This supports our decision to employ the ESOM task to test the engagement of circuitry of self-processing and affect regulation (right amygdala or dACC-mPFC FC) after neurofeedback training. The current version of this task has been programmed in E-Prime.

Emotion Regulation (ER) task. This task resembles a task used to modulate affect via NF in BPD patients [43]. It entails viewing 3 blocks of emotional images (2 negative and 1 positive) and 1 block of neutral images (image blocks duration = 70 secs, task time~13 min). Participants will increase their positive affect during positive and neutral blocks and decrease their negative affect during negative blocks in a "regulate" condition using any regulatory strategy of their preference. During a "passive" condition they will observe the images naturalistically. Standard images are drawn from the International Affective Pictures System [44,45]. Self-injury images were gathered from pictures participants have posted online [46]. Our data on image ratings indicated that all participants rated such images similarly. Participants will report affect regulation strategies used and rate images on a scale of 1-5 for arousal and valence after the scanning session. Dr. Quevedo has administered this task to healthy and self-injurious participants [47]. As noted in our pilot data section, it yielded significant amygdala-cortical FC differences for self-injury versus negative images between healthy and self-injurious participants. The current version of this task has been programmed in E-Prime.

Implicit Association Test, IAT [38,39]**.** A computer-based test that uses reaction times for word classifications to measure self-relevant associations about life and death/suicide. Participants will classify stimuli representing the constructs of "death" (i.e., die, suicide) and "life" (i.e., alive, thrive) and the attributes of "me" (i.e., I, myself, self) and "not me" (i.e., theirs, other). RTs are recorded and an IAT score indexes association between "death" and "me." A positive IAT score indicates stronger association between death and self (i.e., faster RT to the "death"/"me" blocks vs. "life"/"me" blocks). A negative IAT score indicates stronger association between life and self [38,39].

Emotional Testing Battery, ETB [40]**.** The ETB is comprised of computerized tasks that assess emotional processing and affect regulation. The facial expression recognition test (**FERT**) entails recognizing six different facial expressions of varying intensity in random order. It yields accuracy and reaction times across positive and negative expressions. The emotional categorization task (**ECAT**) tests response speed to positive and negative self-descriptors that participants categorize as something they would like or dislike to overhear someone saying they possess. Reaction times for positive descriptors are the outcome. The emotional recall task (**ERT**) takes place 15 mn after the ECAT. Participants recall as many descriptors as possible. Recall accuracy and intrusions of positive vs. negative descriptors are the outcomes. The faces dot-probe tasks (**FDOT**) present images of emotional or neutral faces followed by a probe to select the correct orientation of the faces (vertical vs. horizontal). Faces are presented as either masked, i.e., too fast for conscious processing, or un-masked. The outcome is vigilance scores calculated by subtracting reaction times from trials with probes in the same positions as faces (congruent) from trials where probes appeared in opposite positions as faces (incongruent).

Table 1 (11-18 years old). Patients with BPD (17-45 years old) **may complete only 4 sessions**. Several weeks may separate visits and additional visits may be scheduled to complete unfinished procedures. Order and day of procedures administration can be altered by adding additional visits or flexibly to accommodate participant's needs.

Visit 1: Baseline	**Visit 2: Scan day 1**	**Visit 3: Scan day 2**	**Visit 4: Post-NF**	**Visit 5: Approximately 1 Month later after Visit 4.**	**Additional visits as needed to complete pending tasks**
KSADS. Children Depression Rating Scale-Revised (CDRS). Difficulty with Emotion Regulation Scale (DERS) [23]. Self-Perception Profile for Participants (SPPA) [24,25]. Responses to Depression (RD)[48]: rumination.	SIQ, BDI, DERS, SPPA, RD Medication, psychotherapy. Review 5 happy memories.	SIQ, BDI, DERS, SPPA, RD Review 5 happy memories.	SIQ, BDI, DERS, SPPA, RD.	SIQ, BDI, DERS, SPPA, RD Online	Anything pending
Columbia-Suicide Severity Rating Scale, **C-SSRS**, [49]. Suicide Ideation Questionnaire, SIQ [29].	ESOM: 14 min ER: 13 min	**NF Training:** ESF_NF ~ 44.32 min	C-SSRS, CDRS	KSADS-COMP and C-SSRS	Anything pending
Beck Depression Inventory, BDI[27]. Child Trauma Questionnaire, CTQ [28]	**NF Training:** ESF_NF~ 44.32 min	ESOM: 14 min ER: 13 min	IAT and ETB		Anything pending
Wechsler Abbreviated Scale for Intelligence, WASI[50]. Edinburgh handedness inventory. Write/ discuss 5 happy memories.	30 min break	30 min break	Medication, psychotherapy	Medication and psychotherapy	Anything pending
Medication, psychotherapy, demographics, and puberty stage [51].					Anything pending
Implicit Association Test (**IAT**): Abnormal Self-Processing Behavior [38,39]. Emotional Testing Battery (**ETB**): Affect and self-processing [40], or another similar test. **Can be administered also before scanning on scan day 1 or after scanning on scan day 2.**	Ease of recall rating. SIQ, BDI, DERS, SPPA, RD.	Medication, psychotherapy. Ease of recall rating. SIQ, BDI, DERS, SPPA, RD.		IAT and ETB	Anything pending

- Items from the KSADS, C-SSRS and Medication and psychotherapy forms will be shared with the IMM to confirm inclusion vs. exclusion of participants.

Remote-Research Procedures: Visits 1, 4 and 5 and some aspects of visits 2 and 3 can be conducted remotely via on-line platforms. We will use Zoom for video contact with participants and their caregivers to conduct assessments such as the K-SADS and other interview portions. This protocol requires recordings of interviews and diagnostic assessments, which will be captured using Zoom. If other platforms become available for research use as they are currently approved for remote clinical services throughout the University (e.g., Skype or DOXY), we may seek IRB approval to expand our options within this protocol. If due to unforeseen difficulties, we are unable to use Zoom, we will inform the IRB and the CTSI monitors or any deviations.

In those cases, the videos and personal health information (e.g., name, phone numbers) will be saved in a secure AHC server, on Box, or copied to DVD's or external drive and stored in locked secure rooms at the University of Minnesota, Department of Psychiatry. Only study personnel will have access to such rooms. After transferring this data to those secure locations, staff will delete and purge the trash from all information from terminals (in very infrequent cases) or study computers. The project manager or the experimenter in charge of the interview/procedure will be responsible for immediate transfer of the data from their terminal or study device (if remotely taping interviews/conducting research procedures) to the secure storage areas/DVD's or external drives which will be password protected, and of entering or transporting the data to a secure on-line database or locked room. Any device expected to be used to temporarily store participant videos or pictures will undergo security review before use.

All data will be de-identified and labeled only by participant identification (ID) numbers. These databases will be stored separately from the identifying personal health information and from signed consent and assent forms. De-identified databases will be kept in the PI passworded secure google drive (the PI will grant access to Investigators and the PI, or the project manager will remove them from access to the shared directories when they no longer work in the project).

De-identified data sets and ID coded information will be kept in the Minnesota Super-Computing Institute (MSI) or at the center for magnetic resonance research (CMRR) servers which are also secure password protected directories. These remote-research visits will pertain to procedures such as questionnaires, interviews, or tasks that could be performed online or via the phone in case it is not advisable or possible to interview participants in person. For example, during national health emergencies (e.g., the CONVID19 pandemic) **or if the participants and their families cannot attend in person.**

Remote research procedures: Alternatives may include administering some of the tasks as online secure questionnaires or tasks so that the participants can complete the study from the comfort of their home. Participating Participants could ask parents, caregivers or friends of the adolescent (depending on participant's comfort with the person taking the picture) to take their pictures and the participating participants or their caregivers will email /text the pictures to the experimenters, who will save this information in a secure server and immediately delete and purge the email or text containing the participant's pictures from the study email or the experimenter's email/phone. Please see consent form about email and text communications between participants and research personnel.

There might be use of REDCap enabled tasks and questionnaires or communication/uploading of participant's pictures via a similarly secure platform (e.g., via the Minnesota Super-computing Institute) when remotely working with participants. We are preparing for this possibility, but participants could be asked to email or text their pictures to the study staff to ease communications as not all families or participants are familiar with REDCap or with similar platforms. The additional risks of transmitting this information will be clearly stated in consent and assent forms. Finally, other online protocols will be followed if and whenever possible, for example we might use the library of available instruments via Vanderbilt University: https://redcap.vanderbilt.edu/consortium/library/search.php

5.1 **Study Procedures: NF = Neurofeedback:** Noninvasive modulation using inside the scanner to visualize activity within specific areas within the brain. Participants see their brain activity in real time and attempt to increase or decrease the depicted activity by engaging in specific mental activities, e.g., recalling positive memories. Related region means a region (ACC or Amygdala) which enable memory recall, Unrelated region means a region that does not relate or supports memory recall. Please note that very similar study procedures were previously approved by the U of M IRB under study 1502M63041.

Missing Data, Questionnaires and Tasks: Participants have the right to leave portions of tasks or instruments unfinished if they do not wish to answer the questions. **This is expected in any psychosocial research. This is not a protocol violation but a natural adaptation of the study procedures to the participant's wishes and status during the research.** All efforts will be made to complete items, questionnaires, and tasks while the study is active, and with the parents and the participant's consent. If participants are tired, they can either take some of the questionnaires and tasks at home, complete them remotely, or with the aid of researcher and staff personnel trained in clinical procedures for reconstruction of emotional and cognitive memories to finished questionnaires completed later. All efforts will be made to complete pending questionnaires and data via remote or in person contact with participants and their parents. Dr. Quevedo, the PI, has experience with longitudinal research to recover missing data with the use of memory prompts and adequate clinical interviewing techniques like the ones employed for completing the K-SADS and the Mood Timeline which rely on the participant's memory of past symptoms and experiences. Questionnaires/tasks that need to be recovered will be administered and adapted to use clinical interviewing techniques that allow participants and their parents to recall the time period targeted by the study (**5-12 months**). Modified instructions for recovering those questionnaires and procedures to be uploaded later. **True missing data**, i.e., data that cannot be recovered or which is truly missing at the end of the data collection period, will be either statistically imputed (i.e., missing values will be estimated from available data or mean values will be used) or eliminated from analyses at the time of data analyses during the writing of papers.

Some of these items/questionnaires (ex, 18a and 18b and 18c) measure the same construct. We are aware of participant burden and in most cases will not use all of them. We would like approval or consideration for multiple measures to select from. In cases where there is a short form of the measure available, the short form will likely be used. We will also adapt the item used depending on the child's developmental stage (for example CDI for younger Participants and BDI for older Participants).

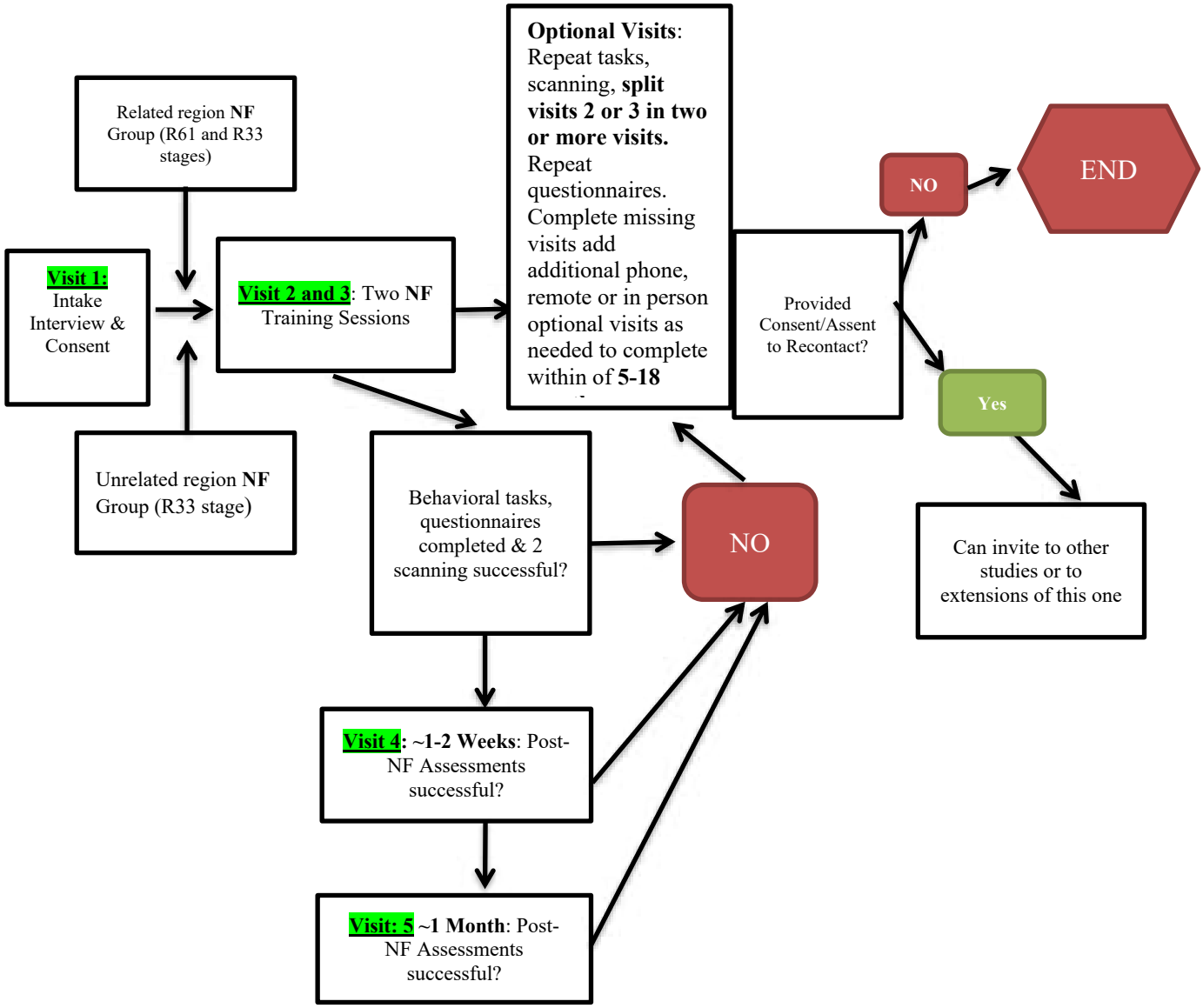
Study Item	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Optional contact visits/phone/remote video/in person.**
1.Informed consent process Assent and consent forms. **HIPPA** form.	X					X
2. Current medications and Therapy. Release of Information (as requested by each hospital)	X	X	X	X	X	X
3. Columbia-Suicide Severity Rating Scale, **C-SSRS,** [49]	X			X	X	X
4. Facial photographs	X					X
5.Children's Depression Rating Scale (**CDRS-R**)	X			X	X	X

6. Mood Timeline	X				X	X
7. Wechsler Abbreviated Scale of Intelligence (**WASI**)	X				X	X
8. Suicide Ideation Questionnaire. About My Life (**SIQ-HS**)	X	X	X	X	X	X
9. Schedule for Affective Disorders and Schizophrenia for Children (**K-SADS**)-COMP or in paper	X				X	X
10. Adolescent Dissociative Experiences (**A-DES**)	X	X	X	X	X	X
11. Perception Profile for Participants (SPPA)	X	X	X	X	X	X
12a. Beck Depression Inventory (**BDI**-II) Questionnaire 12b. Children's Depression Inventory (CDI)	X	X	X	X	X	X
13. Behavior Assessment System for Children, 2nd edition (**BASC-2**)	X				X	X
14. BIS/BAS	X			X	X	X
15. Child Trauma Questionnaire (**CTQ**)	X				X	X
16. Children Attributional Style Questionnaire (**CASQ**)	X	X	X	X	X	X
17. Conflict Behavior Questionnaire Adolescent (**CBQ**)	X			X	X	X
18a. Deliberate Self Harm Inventory (**DSHI**) **18b.** Self-Injurious Thoughts and Behaviors (**SITBI**) **18c.** Inventory of Statements About Self-Injury (**ISAS**)	X	X	X	X	X	X
19. Difficulties in Emotion Regulation Scale (**DERS**)	X	X	X	X	X	X
20. Difficulties in Emotion Regulation Scale – Positive (**DERS-Positive**)	X	X	X	X	X	X
21. Edinburgh Handedness Inventory	X					X
22. Mood and Feelings Questionnaire (**MFQ-KID**)	X	X	X	X	X	X
23. Multidimensional Personality Questionnaire (**MPQ-EZ**)	X				X	X
24. Peterson Puberty Scale (**PPS**)	X		X		X	X
25. Responses to Depression (**RD**).	X	X	X	X	X	X
26. Tanner Puberty Scale	X				X	X
27a. **SSSC** Child Interests and Preference Test. **27b. UPPS-**Impulsive Behavior Scale	X				X	X
28. CES-D Parent About Self	X		X		X	X
29. Conflict Behavior Questionnaire: Parent Version. (**CBQ-P**)	X		X		X	X
30. ESM-Parent Questionnaire	X		X		X	X
31. Health and Resources Questionnaire	X			X	X	X
32. Life Events Questionnaire – Parent	X			X	X	X
33. Multidimensional Personality Questionnaire (**MPQ-GEN**)	X				X	X

34. Minnesota Multiphasic Personality Inventory (**MMPI-2 RF**)	X					X
35. Psychopathology of 1st Degree Blood Relatives – Parent	X			X	X	X
36. Scan including the Emotional Self Other Morph (ESOM) test and neurofeedback using the ESOM task and the emotion regulation (ER) tasks: already described.		X	X			X
37. Phone follow-up **if permission granted by participants. Submit later.**						X
38. Modified Scale for Suicidal Ideation (MSSI) – to be used as needed e.g., for triage evaluation acute suicide risks in addition to the C-SSRS	X	X	X	X	X	X
39. UCSD Brief Assessment of Capacity to Consent (**UBACC**)	X					X
40. Anxiety Timeline	X			X	X	X
41.Peterson Puberty Scale.PPS-Male	X			X	X	X
42a. Self-Compassion Scale **(SCS)** **42b. the Self Compassionate Reactions Inventory.**	X			X	X	X
43. Adolescent Life Experience Survey	X			X	X	X
44. Hopelessness Scale for Children (HSC)	X	X	X	X	X	X
45a. Dimensional Anhedonia Rating Scale **(DARS)** **45b.** Temporal Experiences of Pleasure Scale **(TEPS)** **45c.** Positive and Negative Affect Schedule **(PANAS)**	X		X	X	X	X
46. Brown_Stanley Safety Plan Template	X			X	X	X
47. Suicidal Circumstances Schedule	X			X	X	X
48. Suicide Attempters Risk	X			X	X	X
49. Suicide Attempters Intent	X			X	X	X
50. Phone suitability screen script						
51. Rosenberg's Self-Esteem Scale (RSES)	X			X	X	
52. Dissociation Experience Scale (DES-2)	X	X	X	X	X	
53. Dissociation Tension Scale (DSS)	X	X	x	X	X	
54. Borderline personality questionnaire (BPQ)	X			X	X	
55. Revised Conflict Tactics Scale (CTS2)	X					
56. California Psychotherapy Alliance Scales (CALPAS)	X					
57. Working Alliance Inventory (WAI)	X					
58. Working Alliance Inventory – Short Revised (WAI-SR)	X					
59. Experiences in Close Relationships-Revised (ECR-R)	X			X	X	
60. Structured Clinical Interview for DSM-5 Personality Disorder (SCID-5-PD)	X			X	X	X

61. Structured Clinical Interview for DSM-5 Clinician Version (SCID-5-CV)	X			X	X	X
62. Minnesota Multiphasic Personality Inventory-Adolescent (MMPI-A- RF)	X			X	X	X

Study Duration: **Approximately 5 - 18 months**.



5.2 The duration anticipated to enroll all study participants: 5 -10 years.

5.3 The duration to complete all study procedures, long-term follow-up, data analysis: 14 - 20 years.

5.4 Use of radiation: No use of radiation.

5.5 Use of Center for Magnetic Resonance Research: Yes.

6. Data and Specimen Banking: N/A.

6.1 Not applicable.

7. Sharing of Results with Participants

7.1 Results will not be shared with participants unless guardians/parents/caregivers specifically request them in writing (via email to the PI). If so, a summary of key questionnaires, (i.e., one paragraph) will be emailed to the caregiver from queve001@umn.edu. No unscored or "raw" protocols will be shared to preserve test integrity and to avoid confusing patients or

their families about the meaning of the tests. Psychological findings and results are not recommended to be disseminated in the absence of a feedback session with a licensed mental health practitioner. However, if there are unexpected findings in the brain imaging (e.g., possible brain tumor or cyst evidence in the structural scans) the entirety of the brain imaging acquisition will be shared with the participant and their family (in a cd directly given to the parent/caregiver) and they will be instructed to consult with a radiologist and/or neurologist. The costs of that consultation are not covered by this research.

7.2 Sharing of genetic testing: **N/A.**

8. Study Population

8.1 **Inclusion Criteria**:

a) 1st-time suicide attempting participants (11-18 years) with current suicide ideation. However, if within the first 3 months of the project starting participant recruitment it is difficult to recruit the targeted number of participants, **the study population will be expanded to any suicide attempting participants without restricting to 1st time attempters, and we could also include first time attempters with low or no suicide ideation**. This flexibility to recruitment criteria is implicit in our protocol if recruiting 1st time attempters with lingering ideation proves to be very difficult.

We will also include participants with any level of depression and: 1. current suicide ideation, 2. no current suicide ideation but a history of past suicide ideation, 3. neither past nor present suicide ideation.

History of suicide attempts, suicide ideation, and depression levels will be ascertained during the phone screening. During the first session, suicide ideation levels will be ascertained using the suicide ideation questionnaire or a similar approved short questionnaire. Any criteria not specifically coded for by the BPIC will be tested by study and the research staff, e.g., IQ and handedness. If targeted clinical population participants become 18 during the project, they will be re-consented with the adult consent form.

b) Adult individuals (18 -45 years old) with Borderline Personality Disorder (BPD) symptoms or youth with BPD traits (17yrs.) regardless of their history of suicide ideation or attempts.

8.2 **Exclusion Criteria:** Please see Table 2.

Table 2. Inclusion and Exclusion Criteria

Inclusion R61-R33	Exclusion R61-R33
a) 11-18 years old, right or left-handed, gender balanced participants. Depressive Disorders, PTSD. 1.Suicide ideation ~1 standard deviation in the suicide ideation questionnaire [29] and/or a suicide attempt (within the last year or at any time in their life). 2. Depressed participants regardless of their history of suicide attempts with any current or past levels of suicide ideation. Comorbid anxiety disorders, eating disorder symptoms & experimental substance use allowed. Stable medication and therapy allowed (~ 2 weeks of treatment), however the latter can be relaxed to increase accrual.	MRI contraindicated (e.g., claustrophobia or pacemakers or other metal implants incompatible with MRI). History of traumatic brain injury. IQ<75. Severe or acute medical illnesses that require multiple hospitalizations. History of severe brain damage, frequent/current seizures, mental retardation, or serious neurological disorder that affects brain structure. Previous history or current diagnosis of Schizophrenia, or Autism. Refusal to cooperate with study procedures. High acute, imminent suicide attempts risk. Please see the **Suicide Risk Assessment** section for criteria to determine this risk. Pediatric Psychiatrist, MD, and Dr. Quevedo, PhD. will consult each other and triage the need for hospitalization, emergency room escort, and medication adjustment for participants with acute suicide risks. An additional level of safety may include "on-call" mental health workers that staff can consult to determine exclusion. A current diagnosis of a substance use disorder. Primary psychotic disorder or active psychosis. Active substance abuse disorder or primary diagnosis of anorexia disorders. Symptoms of anorexia disorders are not considered exclusionary criteria.
b) Adult individuals (18-45 years old) with Borderline Personality Disorder (BPD) symptoms or youth with BPD traits (17 yrs.)	MRI contraindicated (e.g., claustrophobia or pacemakers or other metal implants incompatible with MRI). History of traumatic brain injury. IQ<75. Severe or acute medical illnesses that require multiple hospitalizations. History of severe brain damage, frequent/current seizures, mental retardation, or serious neurological disorder that affects brain structure. Previous history or current diagnosis of Schizophrenia, or Autism. Primary psychotic disorder Refusal to cooperate with study procedures. High acute, imminent suicide attempts risk. Please see the Suicide Risk Assessment section for

	criteria to determine this risk. Psychiatrist, MD, and Dr. Quevedo, PhD. will consult each other and triage the need for hospitalization, emergency room escort, and medication adjustment for participants with acute suicide risks. An additional level of safety may include "on-call" mental health workers that staff can consult to determine exclusion.

Healthy control 11-18 year old Participants (N~ 15) volunteers, balanced in gender who do not meet any of the criteria for diagnostic risks (i.e. no current psychological illness or past history of suicide attempts) will be included in the initial stage of the research to train personnel and test the procedures in healthy participants, while PI and research staff leads all procedures, prepare data sets and pipelines and while recruitment procedures and community contacts are developed by the researchers. Healthy adolescent volunteers may not be compensated but recruited from the community to voluntarily participate to advance neuropsychological research. If monetary compensation is required (e.g., due to the burden of the tests and days/hours the participants and their family is involved or preferred by the healthy volunteer and their family, it will be at the indicated lower rates in the compensation section. Healthy volunteer data will be used for data analyses or publication if of enough completion, quality and/or sample size.

Similarly, **healthy adult volunteers** – accrued via the CMRR adult volunteer program or recruited among study adult volunteer graduate or undergraduate students or in the general population (but using the present IRB protocol) will be included in the initial stages of the research to train personnel, analyze data and pilot the data collection procedures. Healthy adult volunteers will include the PI (Dr. Quevedo) who will pilot the fMRI tasks and all the tasks by herself without compensation. Healthy adult volunteers could be undergraduate research assistants that will volunteer without monetary compensation due to their interest in the research itself or in exchange for research credit/hours at the University of Minnesota or in any local University.

9. Screening

We will accrue a data set of participants (ages 11-18) across levels of suicide ideation, defined as **SIQ** [29] total score or other similar approved questionnaire that can be quickly administered over the phone or during the first session. History of suicide attempts will be identified at recruitment and confirmed later with an in-person interview using the C-SSRS, [49] and the K-SADS, [26] and other suicide ideation questionnaires. Caregivers will complete questionnaires about children and about themselves, they are included in the research even if they have medical psychiatric conditions. Parents **are not** the focus of the research, but they will provide information about their own mental health history, their children's mental health history, some of the parent's current symptoms if applicable and their relationship and the rearing environment. We will also recruit adult individuals with symptoms of Borderline Personality Disorder (BPD) or youth BPD traits (17 yrs.)

10. Vulnerable Populations

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
1.Children	Targeted Population
2. Pregnant women/fetuses/neonates	Excluded from Participation
3.Prisoners	Excluded from Participation
4. Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
5. Non-English speakers	Included/Allowed to Participate
6. Those unable to read (illiterate)	Excluded from Participation
7. Employees of the researcher	Included/Allowed to Participate

8. Students of the researcher	Included/Allowed to Participate
9. Undervalued or disenfranchised social group	Included/Allowed to Participate
10. Active members of the military (service members), DoD personnel (including civilian employees)	Included/Allowed to Participate
11. Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Targeted Population
12. Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, transportation, or healthcare.	Included/Allowed to Participate
13. Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to Participate
15. Individual or group with a fear of negative consequences for not participating in the research (e.g., institutionalization, deportation, disclosure of stigmatizing behavior).	Included/Allowed to Participate
16. Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Included/Allowed to Participate

10.1 **Additional Safeguards**: A data safety and monitoring board (DSMB) and an independent medical monitor, specifically Presently, **an independent medical monitor** IMM) will monitor the research procedures and the safety of the participants. Please see the attached data safety and monitoring plan (DSMP) uploaded in ETHOS.

Please note that regarding Table 9 Vulnerable Populations: The following assurances apply to all of them, they will be informed of the risks and benefits of the research, their information will be kept confidential, and they will have freedom to decline and withdraw from the research at any point. Their inclusion and participation will be subject to the monitoring by a DSMB and an IMM. The inclusion of adults lacking capacity to consent and/or adults with diminished capacity to consent, members of the military or disadvantaged individuals is made to provide for assurances regarding the participant's parents. While parents are not the focus of the research, they will be asked to complete questionnaires about themselves and about their offspring.
Regarding Population (1) Children. Consent from parents/caregiver will be obtained via a signed consent form and clear concise verbal explanation of the research goals, procedures. Participant's confidentiality will be assured but parents and their children will be informed of limitations of confidentiality regarding danger to self, others, and impending risks of suicide attempts. Meaningful assent via a signed form will be also obtained from the Participants. Only one parent or caregiver will be needed to provide consent. If the adolescent turns 18 while still in the study, they will sign a consent form in the next scheduled visit before any further research procedures take place. Participants and their families will be informed of their freedom to decline and withdraw from the research at any point without penalty. Participants and the parent/caregiver will sign a HIPPA form to grant access to medical records, this might also be an additional form that is standard to each clinic and will be uploaded to ETHOS in addition to the HIPPA portion in the consent/assent forms.
Regarding Population (5.) Non-English Speakers only **Spanish speaking participants and parents** will be included as the PI's Dr. Quevedo's first language is Spanish. Please see the consent section for procedures to be followed with this population. The same assurances regarding confidentiality, freedom to withdraw and monitoring apply to all participants. Participants need to be able to speak and read English fluently and/or be bilingual Spanish/English speakers to be included, parents who speak limited English but who primarily speak Spanish can be included.
Regarding Population (8.) Students or Employees students and research assistants and employees will be allowed to participate as pilot adult participants if they wish it. This will not be a condition for their accrual of research credits, for their continued

employment, or for their participation as research assistants or employees in research conducted by Dr. Quevedo at the University of Minnesota. The same assurances regarding confidentiality, freedom to withdraw and monitoring apply to all participants. The CMRR has a pool of adult volunteers to test emerging protocols and healthy adult volunteers may be reached to pilot the research. **Regarding Population (11.) Individual or group in stressful situations**. Participants and/or their parents will be approached for respectively contact information of their parents and information to call and offer the opportunity for participation. Clinical or research personnel will extend permissions to contact to participants and/or their parents. The permission to contact documents will also be included in the folder that families review during admittance to emergency room or inpatient units. Both participants and their parents may be approached while participants are in inpatient units or in emergency rooms by clinical personnel or by research staff (after been assured by the clinical personnel of their suitability for research). However, all care will be taken so that Participants and their parents understand that quality or provision of care is independent and unaffected by their decision to participate. The same assurances regarding confidentiality, freedom to withdraw and monitoring apply to all participants. Additional safeguards in this study may include assessment of suitability for inclusion in the present research by an independent medical monitor (an accredited mental health provider). Establishing independent capacity to consent assessment will be done using the UBACC for adolescent participants over 18. For participants under 18, the teach-back method may be used during the consent process to establish the parent's and child's understanding of the study. Please see the **DSMP uploaded in ETHOS**. We will also ensure confidentiality as well as ensure that potential research participants are free to decline joining the study or drop out at any point.

Regarding Population (12.) Individual or group that are disadvantaged. Participants and/or their parents will be provided with a form to provide consent for the staff arranging transportation for research participants during the screening process and at any point throughout the study during which participants or parents are not able to provide transportation. The study team can arrange transportation for research participants via a 3rd party vendor (including but not limited to Taxi services, Uber, Lyft, or an airplane ticket).

- **This study's significance** rests on the relevance of our clinical target for life-span suicide risks. If successful, this project: (i) will yield an intervention to be used alone or in combination with current pharmacological or psychological interventions; (ii) could be expanded and tested with other financially viable biofeedback modalities; (iii) will increase knowledge of neurobehavioral mechanisms of NF's effectiveness to elicit corrective neuroplasticity in circuitry of affect regulation and self-processing; (iv) will inspire new therapies to modify self-processing and affect regulation across diagnostic categories.
- Participants with a recent suicide attempt and occasional suicide ideation are the least impaired participants among which a novel neurofeedback non-invasive treatment of suicide ideation can be tested. Participants who are still acutely suicidal (who report concrete, impending and clear plans for suicide attempts and who cannot commit to not attempting suicide) are excluded from the study as their needs for hospitalization and immediate treatment supersede the aims of this study. They can return to the study after the acuity and risk diminishes. Similar risks apply to adult individuals with a Borderline Personality Disorder (BPD) or BPD traits patients (18-45 yrs.).
- A later section discusses the risks that this research entails. Briefly, participant's confidentiality will be preserved, participants and their caregivers will be free to decline to participate and will have the right to withdraw at any time without penalty. Parental consent and adolescent assent will be obtained via a signed assent and consent forms.

11. Local Number of Participants

11.1 Local Number of Participants to be Consented:

R61 phase. During the 2-year R61 phase, we anticipate screening **~470 participants including ~70 adults** using standard MRI eligibility questions and screening for suicide ideation and attempts. **A maximum of 150 participants** will agree to participate and will undergo baseline tests and pre- NF training tasks. Some attrition is expected due to movement and treatment discontinuation. **60 participants are the minimum** that will allow data analysis and complete all post-NF assessments and 1-month follow-up assessment, yielding 20 data sets per NF target with high quality scans and pre and post NF training data in the R61 phase.

R33 phase. We anticipate screening **~700** contacts for MRI eligibility over 3 years in the R33 phase. We expect that approximately **300 Participants may** perform baseline evaluations and pre-treatment tasks and to garner ~90 high quality scans for all NF sessions randomly assigned to active (**dACC or Right-Amygdala** depending on research phase) versus Unrelated-NF. **70** (minimal number for analysis) and complete pre and post NF-training phenotypical data and high-quality NF scans.

12. Local Recruitment Methods

12.1 Recruitment Process:

We will seek referrals from the Adolescent Inpatient Units at the University of Minnesota (U of M) MHealth Fairview, from the Washburn Children's and Fairview Clinics, the Minneapolis School Clinics, Children's Hospitals and the Emily Program as well as other mental health institutions in the Twin Cities area including Emergency Rooms. Clinicians within inpatient units will extend brief permission to contact forms to participants or their parents. Clinicians can also point out parents or participants to a Quick Response (QR) code that will trigger a permission to contact the used phone number to initiate the screening process. This method is particularly important to protect clinicians, participants and their family and the research staff from in person close contact in closed units to avoid contagion related to epidemics or other contagion agents.

Clinicians can inform research staff about specific patients that are suitable for research and research staff will then extend the permission to contact to the adolescent or their parents/caregivers. Clinicians will not explain the research in detail beyond what will be posted in the permission to contact forms or flyers. Instead, the contact forms or the Quick Response (QR) code will give researchers permission to call parents or Participants and explain the research over the phone and schedule an in-person or remote video call consent process. Additionally, individuals that might extend permission to contacts or use the Quick Response (QR) code include ER staff, doctors, therapists, social workers, pediatricians, or teachers. Both research staff and other referring personnel that extend permissions to contact or Quick Response (QR) code prompts will limit the effects of coercion by ensuring that patients and their caregivers understand that:

1st their decision to participate or not does not affect the quality or availability of care.

2nd the permission to contact or Quick Response (QR) code prompt is not a formal consent document.

3rd Participants will be told that only their parents or designated adult caregivers can consent to participate on their behalf.

We will also disseminate cards, brochures or small printed materials in pediatric inpatient units and emergency rooms across the Twin Cities describing our study. Additional recruitment approaches will include social media (e.g., Facebook, Pandora, Spotify, or Snapchat click ads) and purchased advertisements on traditional media as well as flyers, posters, and cards available in outpatient, inpatient and emergency care units, and approved recruitment boards.

Communications: Participants and their parents will be able to call, text or email (teenbraintrain@umn.edu) the research staff to express interest in participation or to request additional information using phone numbers such as (612 888-5669, 612-273-9761, 612-626-6952, 612-624-4245, 612-624-4223, 612-624-4410, 612-624-8088) or other previously or currently approved numbers by the department of psychiatry and the IRB. This will also entail the use of software applications (e.g., TigerConnect, Soft-Phone) that allows recruitment, and follow-up, whether the staff are present or not physically at their desks in the University of Minnesota, Department of Psychiatry. This information will be posted in permission to contact forms, and all printed and online advertisement materials in addition to the Quick Response (QR) code. **Note: The consent and assent forms allow for the use of not-encrypted text and email communications to facilitate rapid exchanges between participants and research personnel.**

To handle triage and suicide risk situations participants will be able to call the PI or the pediatric psychiatrist and accredited mental health professionals' private cellphone numbers following protocols and safety regulations supported by their professional relationship with the University of Minnesota. These numbers may be provided as part of the Stanley Brown Safety Plan after consent and assent forms are signed. Families, parents, caregivers and participants will be encouraged to save the emergency study phones as "**Emergency Teen Brain Training**" in their mobile devices so that they can easily reach us and so they can recognize our numbers when we call them to provide crisis intervention during working hours, outside of scheduled study meetings/sessions, for participants already involved in the study if such increased contact or crisis intervention was agreed as necessary in their structured Safety Plan Form (Stanley Brown Safety Plan). The PI and accredited mental health professionals will save the participants number on their cellphone as "TBT-participant ID." The participant would only be identifiable by ID number and no names would be linked to the participants' phone numbers on personal cell phone devices. These means will be used for participants to call the study staff and for the staff to call back

For small logistic steps such as aiding with parking instructions and directions to buildings the research staff might use their personal phones and have the participant's number similarly assigned as "TBT-participant ID." No phone number will be identified with a participant's name, address, or any other kind of personal health information (PHI) in research staff phones. Even after these precautions, all call logs for small logistic steps will be deleted.

Note: Some of the proposed advertisements in the various media are currently not available, we will submit modifications to include new materials in addition to the ones included in the first submission.

Letters will be sent to families of participants with recent attempts from the Fairview Clinics using the Fairview recruitment mailing process. Two forms of permissions to contact will be available, one for parents (to call and explain the research and schedule the

"in-person" consent process) and one for participants (to call their parents and explain the research). Critically, the permission to contact form signed by either the participants or the parents does not mean that they have assented or consented formally or been recruited, and this will be explained to the participants and their parents. Please see **Permission to Contact Forms**.

(1) Participants will self-identify as currently having a recent suicide attempt and current lingering suicide ideation via brochures, posters, and/or business cards posted in the department.

(2) The Department of Psychiatry and Behavioral Sciences provides information about research opportunities for the public on a University of Minnesota webpage. Our study will be listed for public information and interest and include information about the study, including contact information such as inclusion/exclusion criteria, current recruitment status, IRB approval number, and contact information.

(3) The outpatient Psychiatry Clinic in the Department of Psychiatry & Behavioral Health at the University of Minnesota provides patients with the opportunity to indicate whether they are interested in being contacted to learn about research studies or whether they prefer to not be contacted. This is accomplished through the provision of a secure electronic REDCap or paper consent form. Access to the voluntary contact information is managed by the Department of Psychiatry & Behavioral Health and securely stored and accessed by the Institute for Health Informatics Data Warehouse (**BPIC**) at CTSI (UL1TR002494). The department's Research Recruitment Specialist partners with BPIC to request a registry database for specific, IRB approved studies. We are requesting permission to receive this contact information to recruit participants for the present study.

(4) The Psychiatry Research Registry in the Department of Psychiatry and Behavioral Sciences at the University of Minnesota provides 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. Non-Fairview or University of Minnesota patients may also sign a consent to be contacted through the registry. Access to this contact information is co-managed by the Department of Psychiatry Clinical Research Advocate and securely stored and accessed by the Data Shelter Manager at **BPIC** and managed through CTSI.

(5) Fairview Health Services collaborates with the University of Minnesota to offer Fairview patients the opportunity to participate in University of Minnesota research. The Behavioral Health Research Review Committee (**BHRRC**) will review this recruitment request that require additional consult before Fairview approval to use the recruitment mailing process or access to patients seen at the behavioral health treatment unities and clinics is granted. They do not act as a substitute for IRB approval but provide language and approval for PIs that is submitted with the IRB protocol. Potential participants are identified, based on protocol eligibility criteria, from a clinical data repository that houses the records of over 2 million patients. Once identified, Fairview mails the IRB-approved study recruitment letter to its patients on behalf of the researcher.

(6) The Research Recruitment and Outreach Specialist (**RROS**), hired by the Department, describes research opportunities to patients and provides the contact information of interested patients to qualified study staff for which they might be eligible. Potential participants will provide information to the Research Recruitment and Outreach Specialist at the Department of Psychiatry and Behavioral Sciences; the **RROS** will also provide potential participants about the research study and provide contact information or connect the potential participant to the study coordinator.

(7) We will utilize social media accounts (such as: **Facebook, Twitter, Instagram, Tick-Tock, independent website, etc**.) to create an informative space about research opportunities and information about the study. These platforms will also be used to disseminate interim findings and progress with participants. Digital media accounts for the "Health and Emotions in Participants Trajectories (**HEAT**) Lab" will be used for this study. A coordinating website "HEAT Lab" or **TBT** study standing for (**Teen Brain Training**) will describe participation information, including inclusion and exclusion criteria and amount of time to complete study (Note: This may be the department webpage instead of an independent website). The website and media pages will provide study team contact information and IRB approval number. Potential participants will be advised to contact the research team directly via phone, text, 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.

Note: If at the time of this protocol submission we do not have an independent website, we will submit the link to the site in a future modification. **The independent web site will not go live until we have official IRB approval.**

(7) We will use advertisements on digital media platforms to reach our research population via demographic and key words. An interested individual's click will bring them to a link (e.g., a landing page, study website, psychiatry website, and digital media page) which describes the study and has a link to a REDCap survey. The REDCap survey asks for contact information, birth date of the potential participant, and if they have met the criteria to participate in the study. Qualified potential participants will be then contacted and screened for eligibility for the study.

(8) This study will be listed with *studyfinder.umn.edu* and *clinicaltrials.gov*. Clinicaltrials.gov is a governmental website which automatically posts federally funded clinical trials and is outside of the control of this research study. This study may be listed at researchmatch.org, trialstoday.org, or patientwing.com.

(10) We will use a Quick Response (QR) code on all printed and digital materials which will allow potential participants to indicate interest and permission to contact that will enable the study staff to initiate the call to the household to screen the participants and their parents.

(11) The study will post business cards, brochures and/or rack cards in the Department of Psychiatry & Behavioral Sciences clinic space at Riverside, St. Louis Park on established research recruitment boards, and other affiliated clinics and clinical spaces across the Twin Cities such as emergency rooms in a variety of hospitals.

(12) Local clinics likely to encounter participants with the described criteria (e.g., pediatricians, neurologists) will be sent an informational letter describing the study and clinicians will be asked to either extend a permission to contact or/and to provide the study contact information to Participants and their caregivers.

12.2 **Identification of Potential Participants:**

1. Participants and their parents will self-identify in response to posters, mailings, emails, permissions to contact, website links.

2. In clinical or school clinic settings, (e.g., inpatient or outpatient units or emergency rooms, school clinics) clinicians, ER staff or doctors (that are authorized staff) will identify suitable participants (with doctor or clinician's guidance) and they will have the initial contact with potential participants.

2.1. Warm hand-off / referral: It will be possible for ER staff, doctors, school clinicians, interested teachers and in-patient unit mental health staff to do **a warm hand off referral** whereby they introduce or refer the parent or adolescent to the research staff and the research staff extends the permission to contact and briefly explains the research for later follow-up and phone screening. Alternatively, if the adult, parent, or caregiver has time, the research staff can conduct the screening and the initial introduction of the study with the caregiver and agree on a first session date to conclude the consent process.

Medical records will only be accessed after the participants and their caregivers provides an agreement to release their PHI contained in their medical records for research purposes; for example, a patient has documented consent to research on their treatment, intake, or hospital admitting form. (MN Statute 144.334 Subd. 3; Access to Medical Records for Research), e.g., Academic Health Center Information Exchange (AHC-IE).

3. Potential participants could also complete a brief questionnaire online (REDCap Survey) accessible via a Quick Response (QR) code in printed/advertising materials such as the permission to contact to determine whether they are eligible. This information is accessible by the Study Staff and PI who will contact them if they are deemed eligible for the study. **Note**: **The REDCap Survey may be submitted later for approval.**

4. Participants could also call, email, or text the research study coordinator and research staff who will conduct a phone screening for eligibility.

5. The Department of Psychiatry also has an IRB approved database and survey in its facilities that potential participants and their parents may complete to indicate interest in the present study.

6. Healthy adult or healthy adolescent participants' recruitment to pilot all procedures before initiating procedures with Participants with psychiatric conditions. Healthy adults will be identified via the existing volunteer program at the CMRR as well as in social media or by offering the opportunity to participate in exchange for research credits to undergraduate students at the U of M. Recruiting of healthy adult volunteers to pilot data will begin before we recruit and test any patients from clinics around the Twin Cities, including Fairview. Meaning, recruitment of heathy adult controls and Participants will begin once the respective consent/assent procedures are approved by the IRB.

7. Recruitment of clinical patients will not begin until the Behavioral Health Research Review Committee (**BHRRC**) has reviewed the recruitment request and Fairview grants approval to use the recruitment mailing process or access to patients seen at the behavioral health treatment unities and clinics. They do not act as a substitute for IRB approval but provide language and approval for PIs that is submitted with the IRB protocol and will be separate from the recruitment of healthy control volunteers that will pilot protocol.

Recruitment Materials: 1. Permissions to contact. 2. Flyers/posters. 3. Radio and social media ads. 4. Websites links. (See attached copies of some of these materials in ETHOS in the Recruitment section. New materials not yet available will be uploaded later) 5. **Quick response (QR) codes,** 6. Contact cards.

Note: Some website links are currently not available, they need to be built. We will submit a modification and the websites that are not yet submitted will not go live until they are IRB approved.

8. IRB approved database and online/paper survey via the Department of Psychiatry.

9. A Quick Response (QR) code will trigger a permission to be contacted from parents or Participants to be contacted by the study staff, in lieu of a printed and filled permission to contact. This provision is made to facilitate responses from potential participants in situations of great stress that might not have the presence of mind at that moment to fill in a form. This provision also protects all individuals involved from close in-person contact or crowding in the ER or in-patient units that increase risks of contagion for all involved.

In this case, however the restrictions for inclusion and exclusion still apply and the provisions stated earlier: **1st their decision to participate or not does not affect the quality or availability of care. 2nd the permission to contact or Quick Response (QR) code prompt is not a formal consent document. 3rd Participants will be told that only their parents or designated adult caregivers can consent to participate in their behalf by signing a consent form.**

Note: We currently do not have a website link or QR code prompt but as soon as is built we will put in a modification, submit the link, and await permission before they go out live.

13. Payment.

13.1 Clinical population Participants that participate in all or partial visits for data analysis, pipeline processing, training and or preliminary data publication or comparisons will be paid in the following way:

Visit 1-Baseline=$60 + **Visit 2**=$90 +$10(snack) + **Visit 3**=$90 +$10(snack) + **Visit 4**=$100 + **Visit 5**=$100 = **$460 of total base amount**. Participants will receive $10 for snacks in cash or as part of the payment on Visit 2 and 3. Parking will be covered for the participant via a parking voucher or an additional of up to $13 will be added to the total payment of each in-person visit.

Incentive amount for Visit 1-3 will be added to baseline amount for each Visit for participants who have no more than 2 instances of rescheduling total for Visit 1 through Visit 3. The amount of additional compensation will be as follow:

- Zero instance of rescheduling for sessions 1-3: **Total compensation amount =** Base amount + $35 incentive/session 1-3
- One instances of rescheduling for sessions 1-3: **Total compensation amount =** Base amount + $20 incentive/session 1-3
- Two instances of rescheduling for sessions 1-3: **Total compensation amount =** Base amount + $10 incentive/session 1-3
- Three instances of rescheduling for sessions 1-3: **Total compensation amount =** Base amount

The incentive amount for session 1-3 will be included in the total payment of session 4. The total compensation amount (excluding parking) is as organized in the table below:

Table 3: Total compensation amount (excluding parking)

Instances of Rescheduling	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Zero	$60	$90 + $10 (snack)	$90 + $10 (snack)	$100 + $35*3 sessions (incentive)	$100
One				$100 + $20*3 sessions (incentive)	$100
Two				$100 + $10*3 sessions (incentive)	$100
Three				$100	$100

13.2 Healthy/Pilot Participants that participate in most of the visits or who might prefer to be compensated and whose information will be used for data analysis, pipeline processing, training and or preliminary data publication or small group comparisons will be paid in the following way:

Visit 1-Baseline=$40 + $15 (parking) + **Visit 2**=$60 + **Visit 3**=$60 + **Visit 4**=$80+ $15 (parking); **Visit 5**=$80+15 (parking), Total= **$365**. Participants may also receive 10$ -20$ for lunch on Visits 2 and 3.

Students or healthy adults or Participants that wish to volunteer and participate as pilot adult participants will receive hours' credits toward their research credit class for research participation. **Healthy volunteers' adults or Participants that undergo voluntary participation as pilots of 1 or 2 of the sessions or a few of the tasks will not be paid. Healthy volunteers will include the PI, Dr. Karina Quevedo and any healthy adult or adolescent associated to the research effort that wishes voluntarily to undergo the neurofeedback procedure or some of the protocol sections in a purely volunteer fashion.**

14. Withdrawal of Participants

Criteria that preclude study participation or continuation will be disclosed in the consent form.

14.1 Withdrawal Circumstances:

1st High risks of imminent suicide attempts, with intent, a plan and/or other conditions for study enrollment are not met. Participants can re-enroll in the study after hospitalization and/or increased levels of care in outpatient treatment and/or environmental changes (e.g., changes in school or place of residence) that leads to demonstrable stabilization and/or decrease high acute/chronic suicide risks. To re-enroll the PI and the IMM (with possible third opinion of Pediatric Psychiatrist if needed) must agree on the results of the study enrollment/re-enrollment conditions.
2nd Onset of significant psychotic symptoms that clearly impair judgment and ability to assent (e.g., presence of pervasive psychotic mood, visual or auditory hallucinations or other manifestations of disorganized thoughts and judgement). Note: mild, transient psychotic symptoms are allowed within the context of a depressive episode or other diagnostic category, if they do not impair the participant's ability to assent or meet criteria for a full psychotic episode as defined by the K-SADS.
3rd Onset of neurological or metabolic illness known to significantly affect brain function and structure.
4th Onset of substance dependency disorder or new evidence that symptoms are linked to substance use.
5th Onset of claustrophobia resulting in intense discomfort in the scanner that cannot be assuaged with brief anxiety decreasing interventions (e.g., talking to the experimenter/breathing and increasing verbal contact with experimenters between pulses of the scanner).
6th Known or strongly suspected SARS-COVID-2 diagnosis in the family or household or recent (1-3 days) onset of symptoms linked to a contagious illness.
7th Medication related toxicity will result in temporary withdrawal until stabilization of symptoms is ascertained via K-SADS guided assessments and/or improvement is ascertained by their attending physician.

Patients who are hospitalized due to suicide attempt or physical illness will be temporarily discontinued/withdrawn from study participation. Patients can re-enroll and resume study activities after discharge from hospitalization, and/or if they start outpatient mental health services (e.g., medication, higher level of frequency of psychotherapy) that demonstrably lowers acute/chronic levels of high risks of imminent suicide attempt. Alternative conditions to be met for re-enrollment may be other environmental change in the home and/or school environment (e.g., changing schools or place of residence and changing caregivers) that also demonstrably lowers acute/chronic, high risks of imminent suicide attempts (**see Inclusion section**). Patients who are hospitalized at another hospital and whose medication is changed will be offered open continued neurofeedback training (after being discharged from the other hospital or/and involvement in outpatient services that decrease high imminent suicide attempt risks) until they complete the study period. Withdrawal and exclusion circumstances will be stated in consent forms.

15. Withdrawal Procedures.

15.1 Withdrawal Procedures:

Participants will be allowed to withdraw at any point during the study; all that will be required will be an email or a verbal communication via text or phone call or direct communication with any of the experimenters. Already enrolled participants' data will be part of future research and the study may continue having access and use the participant's medical records unless the

participant and/or their parents explicitly revoke our access via written communication (email or letter) or in a phone call or in person conversation. We will ask all participants whether they wish to continue giving the study access to their psychiatric records or not after withdrawal from the study (HIPAA).

15.2 **Termination Procedures**:

Participants and their parents will be called and informed verbally about the causes for termination. Alternatively, a message containing minimal information will be left in their voicemail. A brief, simple email can announce the termination without any details and with instructions to call the research staff for more specific information. Data collected till that point will still be included in research after termination.

16. Risks to Participants

16.1 Foreseeable Risks

1. Suicide attempt or completion risk. Because the focus of this study is an intervention for participants with recent suicide attempts and current suicide ideation, the participants are at increased risk for suicide attempts, increased suicide thoughts and hospitalizations. **Participants who have attempted suicide are more likely to repeat attempts, to be hospitalized or to complete suicide compared to the general population of psychiatric patients**. **It is highly likely that the present study will entail reporting suicide attempts, suicide completions and hospitalizations given the population we are studying. Suicide attempts, completions or hospitalizations are thus a characteristic of the population and not a likely consequence of the proposed intervention which is of minimal risk and intrusiveness.**
2. In person suicide risk will be assessed at baseline and at the post-intervention assessment and additional precautions will be taken to help ensure participant safety. The PI (Dr. Quevedo, PhD, L.P.) will work in conjunction with a designated pediatric psychiatrist at the Department of Psychiatry Child and Adolescent Clinic. Drs. Quevedo or the designated pediatric psychiatrist (if the PI is on vacation or in a conference) will be available to the PI and study staff during each of the clinical assessments, to consult with the study staff regarding the suicide risk, triage, and intervention planning. In addition to these resources, the UMN outpatient clinic has a list of 6 qualified providers that experimenters can call in case of emergency. During in-person assessments, if a 72-hour hold is warranted to ensure participants safety, security personnel are readily available in case experimenters determine that there is urgent need for escorting participants and families to the emergency department (ED) for possible hospitalization and/or further evaluation.
3. Potential loss of confidentiality. All clinical information will be kept confidential in a secure database. Data will be stored using a study-generated identification number. Any documents with personal health information (i.e., consent forms), will be kept in a separate, locked file. Links between participant names and participant numbers will be stored in a secure database with limited access only to select study staff. Information provided by the Participants to study staff will be kept confidential from their parents, except in the case where danger to self or others is identified. In those cases, the parents will be informed, and the participant will be referred to clinically appropriate emergency care.
4. Distress related to clinical assessments and neurofeedback. Some of the questions may be distressing to Participants and young adults with internalizing symptoms because of inducing low levels of negative self-focused cognitions. Additionally, anxious individuals can easily feel overwhelmed or fatigued by what would be minimally demanding tasks for others, such as filling out these assessments. Voluntary neuromodulation is not easy, some participants may feel frustrated or sad due to perceived inability to complete the task.
5. Risks related to MRI

a. *Claustrophobia.* Some people experience fear while inside the scanner due to its confining space.
b. *Magnetic pull-on metal objects.* The strong magnetic field in the scanner could cause any foreign metal bodies implants in the participants to change position, injuring them.
c. *Scanner noise*. The noise generated from the operation of the scanner is loud and can damage hearing without protection.
d. *Mild symptoms.* Some people experience mild, short-term symptoms while in the scanner, including headaches, dizziness, mild nausea, metallic taste, and/or the sensation of flashing lights. These symptoms resolve shortly after removal from the magnetic field.
e. *Boredom.* MRI scans involve a large time commitment, and participants may become bored.
f. *Potential for discovery of brain abnormalities.* It is possible that the MRI scan would reveal unknown and unlooked for abnormalities. We will refer the family to a radiologist (covered by the family's insurance) and provide them with a copy of the structural images if so desired.
g. *Energy from the scanner can cause heating or nerve stimulation.* The power of the energy waves from the scanner is well below the strength needed to heat body tissues and cause harm, but any metal in contact with the participant's skin could cause heating. It is also possible that the scanner will cause peripheral nerve stimulation (stimulation of the nerves or muscles).

6. New psychiatric disorders. Participants will be assessed for a variety of symptoms, and it may be determined that the participant meets the criteria for a psychiatric disorder that they were not already being treated for.
7. Onset or worsening of symptoms due to medication: The population been studied is likely to be taking one or several psychotropic medications. The proposed intervention will not change or manage participant's medications and the investigators will not directly attempt to solve issues related to medication management.

16.2 **Suicide Risk Management in Person.**

Dr. Quevedo, PhD, LP (PI) will always be on call when a participant is being evaluated in person, or she will arrange for other providers (CoI 1 or Dr. Quevedo) to be on call. Additionally, other providers (such as social workers or medical residents) that are generally "on call" could be reached by the staff to evaluate acute suicide ideation (The psychiatry department will internally decide the mechanism about fast communication into the administrating attending).

A psychiatrist or psychologist will be available to the study staff and PI as a consultant if high risk suicidal thoughts or behaviors are identified. The psychiatrist or psychologist will be the key person aiding the PI's evaluation of the need for hospitalization. This individual will complete additional assessment as necessary either by phone or in person. Dr. Quevedo or the psychologists/psychiatrist will collaborate with the study team, participant, and family to construct an appropriate safety plan (Stanley & Brown Safety Plan) and will facilitate referrals for appropriate follow-up psychiatric care. **Figure 1** summarizes the suicide risk assessment and action protocol, which includes comprehensive suicide risk assessment, clinical formulation, and triage, followed by level of care and suicidal risk level determination (see Figure 1).[52] This in-depth assessment will involve the parents to inform them of the current level of risk, gather information regarding the current safety of the home environment and an understanding of current supports, and engage them in safety planning.

If imminent suicide attempt is suspected during the risk assessment, the study staff will contact Dr. Quevedo or the designated psychologist/psychiatrist who will: 1. Contact the participant and their caregivers and re-evaluate intent, plan and lethality using the C-SSRS, the Modified Scale for Suicidal Ideation, and the Stanley Brown Safety Plan. 2. Consult with other providers or with available staff at the University of Minnesota clinic and determine if hospitalization is needed. 3. In the case of significant risk, parents will be informed and involved in the safety planning. All research staff members will be trained according to and follow this protocol.

During in person assessment, emergency medical care (EMC) is available for all research participants at the University of Minnesota Medical Center (UMMC) including security personnel to escort participants and their families to the ED. Participants and their parents will be escorted to the ED by qualified research personnel (The PI, a postdoctoral licensed clinical psychologist, or equally qualified personnel will supervise and conduct these procedures).

16.3 **Suicide risk management for enrolled participants.**

In between study sessions, and as part of the Stanley-Brown Safety Plan, some enrolled participants will be able to call or text the PI (Dr. Quevedo, CoI 1 or any accredited mental health professional) on a cellphone if they feel that the measures in the safety plan are ineffective and they are in impending danger of attempting suicide. Families, parents, caregivers, and participants will be encouraged to save the emergency study phones as "**Emergency Teen Brain Training**" in their mobile devices so that they can easily reach us. The PI and accredited mental health professionals will save the participants number on their cellphone as "TBT-participant ID" (after consent and assent forms are signed) in order to be able to know who is calling and quickly respond. The participant would only be identifiable by ID number and no names would be linked to the participants' phone numbers on personal cell phone devices. Participants and their parents will be told that emergency phone calls/texts will be returned by the PI or the psychologist/psychiatrist within **1 hour** (as the PI, accredited mental health professionals and/or psychologist/psychiatrist may be providing services to other patients); or as soon as the study staff can alert those clinicians or "on call" staffing accredited mental health professionals, of a participant's suicide attempts risks; whichever time frame is shorter. Participants and their parents will be informed of such procedures in the consent and assent form.

However, if the calls, emails, or text are received during the night hours (e.g., after 9 pm) calls/text will not be answered until the next day, and they should call 911 or go to the nearest emergency room to keep themselves safe.

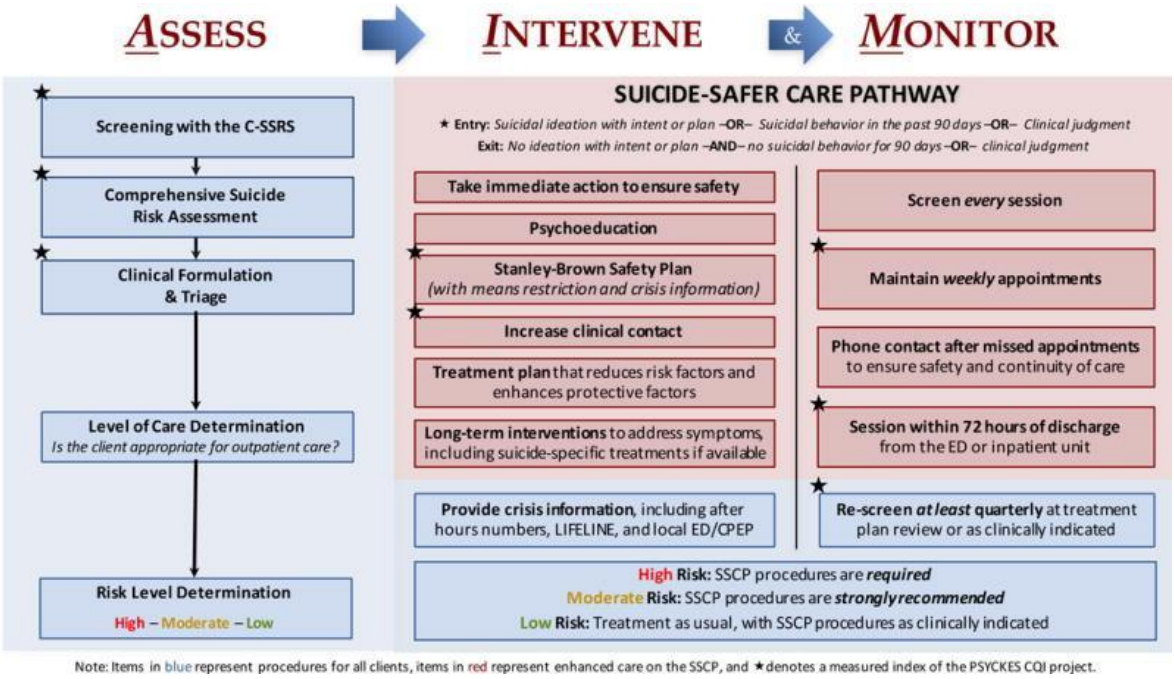


Figure 1: Adapted from Labouliere et al. (2018). This figure provides general guidance for clinicians in charge of at-risk participants. Procedures within a research project are different from some of the assumed timing in this figure because the programmed contact times during the research are different from an ongoing standard clinical practice (i.e., weekly psychotherapy or medication appointments). This plan, however, provides good general guidance for research staff to interact and assess participants' safety while actively enrolled in research.

16.4 Suicide Risk Assessment in Person

Make sure phone numbers, email and emergency contacts are accurate and accessible.

- C-SSRS, [49], all participants (particularly **scores of 4 or 5** in the C-SSRS) require: a) detailed safety planning, b) documentation of protective factors, c) psychoeducation, handling, and documentation of risk factors. (see **Access to Suicide Means**).

- Safety Plan, (Stanley & Brown, 2012), a safety plan with the participants and attending/present caregiver(s). Template – uploaded in the IRB application.

- Protective Factors: Caregivers/parents or legal guardians are **aware of chronically high suicide ideation** (**C-SSRS scores of 4 or 5**). **Caregivers state they can keep their child safe at home despite scores of 4-5**. Document access to adult support (caregivers, teachers, extended family) and family/community support. Caregivers and participants are under the care of a psychiatrist and/or psychologist according to current standards of practice in the community. Caregivers/participants can reach mental health providers and/or know when they have their next appointment.

- Risk Factors: Protective factors are absent. Access to suicide means is unknown or caregivers cannot control them.

Psychoeducation and Assessment regarding Access to Suicide Means.

- Ask caregiver/participants directly about firearms, ensure weapon have been taken care of by another person in the home, store unloaded, dispose of bullets.
- Counsel participants/caregivers to dispose of excess medication. Have another person in the home (caregiver or other family members) dispense medications.
- Encourage families/caregivers to reduce the amount of alcohol stored in the home.
- Ask "what other means for hurting yourself are available in your home?"
- Involve caregivers/parents or legal guardians and extended family members and friends if possible, including those that are not living with the adolescent.

Inclusion (or re-enrollment after hospitalization/ temporary withdrawal) if:

1. **Safety Plan: Able to cooperate with the (Stanley & Brown, 2012) Safety Plan.** Additional positive criteria include details and accessibility of means and persons to enact it. Participants should be able to provide the name of an adult that they can contact if suicide ideation escalates. Additionally, participants should be able to name specific activities or de-escalating regulatory actions to cope with elevated suicide ideation. The credibility of the suicide plan is often indicated by levels of specificity and elaborations in the coping strategies provided. Evaluating a safety plan specificity is a subjective judgment, therefore the ability to cooperate to create a plan is more important than its level of detail as the latter may depend on verbal and communication skills that do not indicate willingness or ability to follow a safety plan.

2. **C-SSRS: Any suicide ideation severity yielded by the (C-SSRS, [49]), Scores 0-5-.**

Category 0 – Absent suicide ideation or attempts
Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal).
Category 10–Completed Attempt (fatal)

3. **Caregivers/parents or adult participants statement of responsibility: If C-SSRS yields scores of 4 or 5 or higher but parents or caregivers or adult participants state that they can keep the participants safe at home.**

4. **Participants statement: Participants can commit to not attempting suicide between the present and the next research encounter.**

5. **Suicide means and psychoeducation. Low to moderate risks during evaluation of access to suicide means.**

6. **Recommendation to parents and additional measures to ensure safety of enrolled participants**

- Caregiver(s) will be recommended to increase the level of care with existing providers or seek them if currently absent. Referrals to the U of M outpatient clinic will be provided to the participants and the caregiver.

- Dr. Quevedo (or the designated psychiatrist or accredited mental health professional) will increase contact with participants/family (call and talk to participants 1 or 2 times a week as needed), particularly if staff becomes aware of periods of high stress, family chaos, increased difficulties at school, bullying, losses, or transitions in care.

- **Document**: risk and protective factors assessment, safety plans, rationale for level of intervention/care.
- When in doubt – consult Dr. Quevedo or the designated pediatric psychiatrist.
- Consult with other providers in the department of psychiatry

7. The Dialectical Behavioral Therapy (DBT: hvalmah@umn.edu) team can be consulted via email 2 weeks before the visit with copy to the PI: queve001@umn.edu

16.5 **Exclusion and triage of in person suicide risks. Risk factors are cumulative, the presence of one risk factor does not automatically exclude a participant. The presence of many risk factors and the absence of protective factors, however, merits considering exclusion from the research.**

Exclusion and referral for increased outpatient level of care or emergency department (ED) assessment for hospitalization if:

- Scores of **4 or 5** or higher in the C-SSRS (**Category 4 - 6**) and:
  - **Caregivers are unable or unwilling to keep the participants safe at home**.
  - Participants show uncertainty (i.e., cannot promise not to attempt suicide) about not attempting suicide between the present and the next research session.
- Inability to fashion a credible Stanley & Brown Safety Plan.

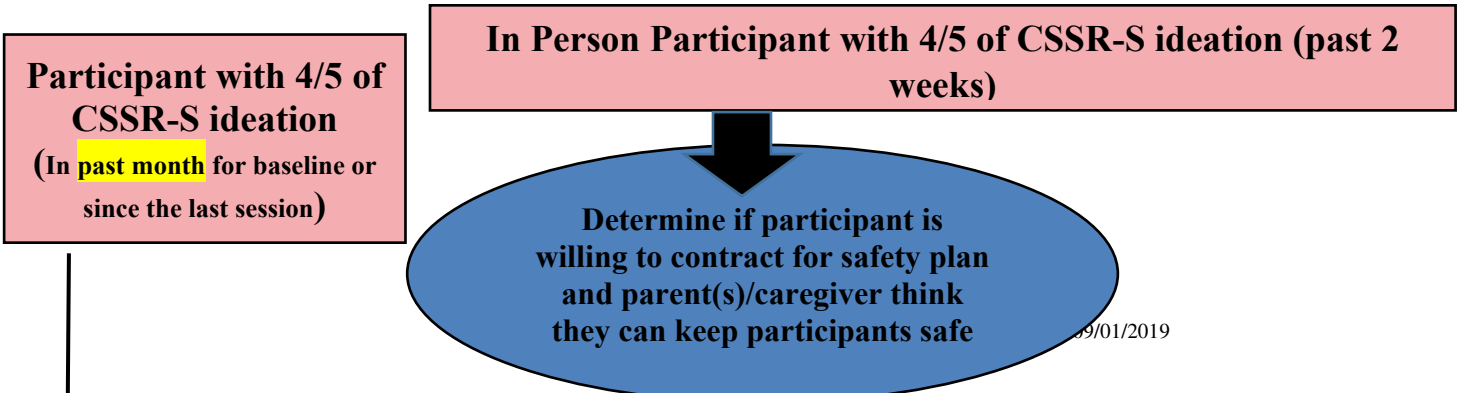
- Determination of high chronic or acute risk due to presence of multiple risk factors and absence of protective factors: e.g., access to suicide means and unreliable or absent control over them.
- In consultation with the "on call" PI or pediatric psychologist this could result in referral for increased levels of current established care or escorting the participants and family to the emergency department (ED) at the U of M.
- Personnel will be trained to conduct and document a safety plan and interview. **The IMM and the PI will review the safety plans after the conclusion of the 1st main interview.**

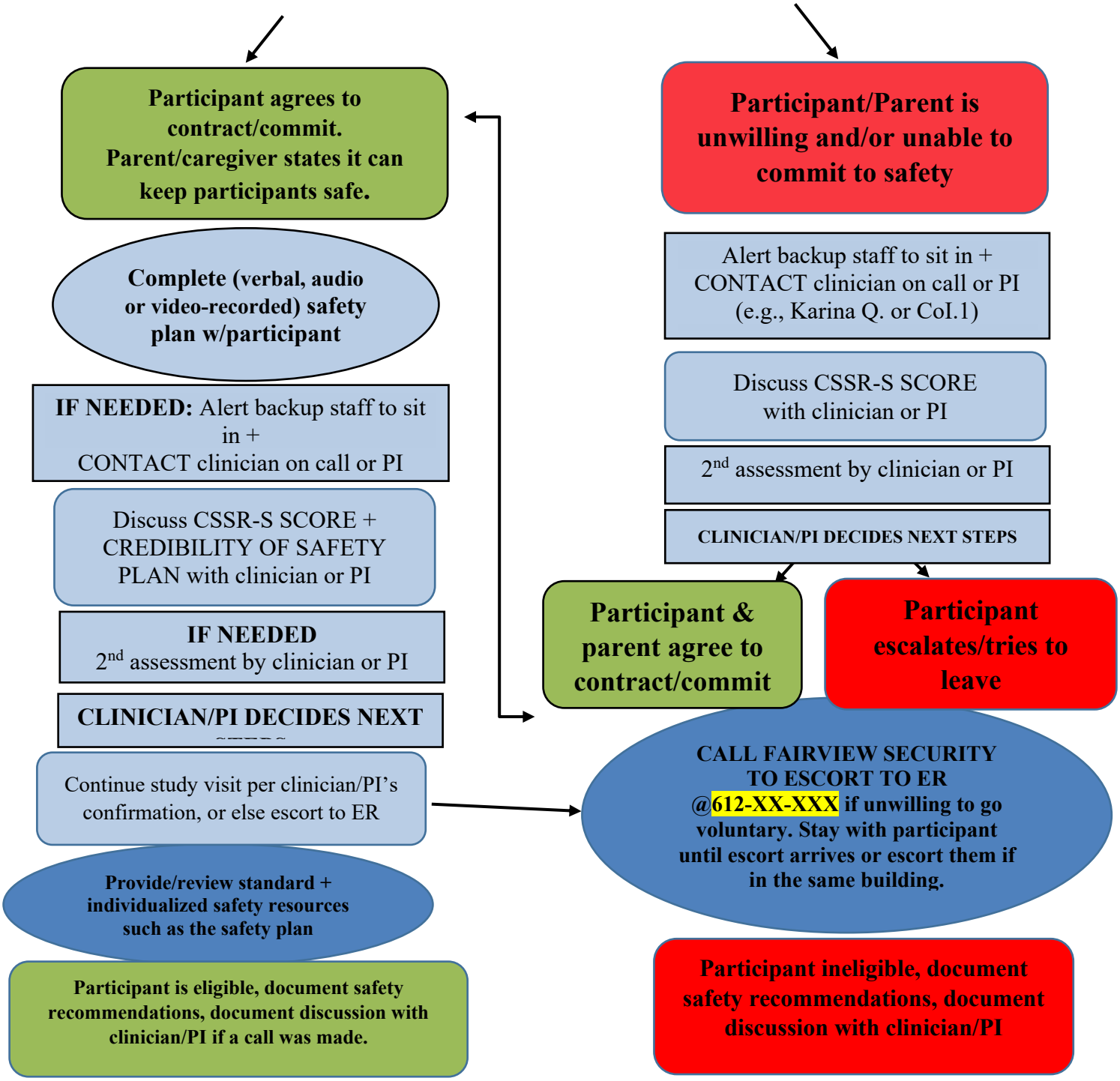
16.6 **Suicide Risk Assessment Remote Participants**

- Before the remote meeting, ensure staff has the correct email address and phone number for both the adolescent and the caregivers and other emergency contacts by calling and emailing them 2 weeks in advance of the remote research section **Participants and their parents/caregivers will program the study phone numbers and emails in their cellphones.** This will be necessary to send the Zoom or other video platform invitation in advance of the visit. Zoom or videoconferencing must be videotaped/recorded for purposes of training, diagnosis, and reliability coding of symptoms among the staff members.
    - The Dialectical Behavioral Therapy (DBT) team can be consulted via email two weeks before a scheduled remote assessment or testing session (moenx008@umn.edu) with copy to the PI: queve001@umn.edu.
- Verify adolescent's location at the beginning of every remote session to ensure emergency services can be deployed if necessary. Obtain the current specific address and location
- Once the remote session starts. Confirm phone number, email and emergency contacts are accurate and accessible.
- Ensure the adolescent is in a reasonably private and safe environment.
- Ensure the caregiver is in the home or readily accessible via phone or text.
- Ensure participants and caregivers can contact research staff easily. If technology issues arise, give them your easiest access number and request/verify theirs and their emergency contact/caregiver's contacts.
- **Use the same guidelines and instruments as the in-person suicide risk assessment.**
- **Lower-level interventions that can be used for C-SSRS scores 1-3**:
- National Suicide Prevention Lifeline: 1-800-273-8255
- Crisis Text Line: Text "Home" to 741741
- Virtual Hope Box (app store)
- Collaborative brainstorming with participants and caregivers to develop/review safety plan.

16.7 **Exclusion and management of remote suicide risks.**

- **If a participant cannot maintain safety or if staff determines that safety cannot be maintained:**
- Caregiver should be contacted and directed to call 911 and/or go to the nearest Emergency Room (ER)
- If the caregiver is absent or unreachable, research staff can call 911 and direct emergency responders to the participants' location.
- **Text, email, zoom, skype, or use any possible means of communication to call staffing "on call" PI or pediatric psychiatrist/clinical before taking the step of calling 911 on the participants' behalf.**





Distress related to clinical assessments or neurofeedback. The principal investigator (PI) and/or trained personnel will always be present to reassure participants and provide support if distress levels become moderately intense. If participants become intensely upset and symptomatic due to the questions and situations involved in the battery of tests and experimental procedures the session will be stopped and, if necessary, discontinued. There are very few Participants who are unable to tolerate the length of the proposed questionnaires and tasks. Nevertheless, breaks and small refreshments might be provided if participants become fatigued during the session. Finally, participants and their parents will be advised that **voluntary modulation is not easy** and that a significant degree of effort is required. Participants will be informed they may be increasing their neural activity on average even if they cannot notice it at each neurofeedback instance.

Confidentiality protection. Identifying information, records, and any audio/videotapes of clinical interactions (if applicable) will be stored in a locked cabinet in a locked office, only accessible to research staff members. A participant's identification number will identify all materials. Participant's identification numbers will be unrelated to participant's characteristics (e.g., date of birth, social security number, gender etc.) in all protocols and instruments. **A list with the pairings of personal health and contact information and participant identification numbers will be kept in secure online database (an excel file inside a secure AHC server: (\\ad.ahc.umn.edu)(S:)\Psychiatry_Share\Psych) or inside a Box Secure Server file that can only be accessed by researchers**. Psychological ratings, test results, and neuroimaging results will be identified with a participant identification number (ID number). These data will be stored in a secure electronic database. To further safeguard the confidentiality and security of data files, computer accounts used to access and analyze data will be password protected when possible. All analyses will exclusively utilize the identifying ID numbers. The PI and all key personnel have completed the University of Minnesota course on The Health Insurance Portability & Accountability Act (**HIPAA**). The research protocol will follow HIPAA regulation to protect the participant's private health information. All study staff will complete training provided on protection of human participants enrolled in clinical research (using resources from CITI-Collaborative Institutional Training Initiative, and other local UMN sources), and on compliance with HIPAA.
Disclosure of health risk behaviors by the adolescent. All participants will be informed during the consent process that their information will be kept strictly confidential unless information is revealed suggesting that the participant or someone else is in danger (e.g., prostitution, IV drug use, child abuse, suicidality, homicidally). Prior to eliciting this information, the adolescent will be fully informed that the research staff may need to report such information. Before parents will be made aware of this information, our procedure will be to first talk with the adolescent and explain what information will be disclosed to parents.

Risk related to the COVID-19 virus epidemic: Face to face contact carries the risk of virus contagion. To protect all those involved, we will make sure that all our staff wash their hands thoroughly before undertaking any procedures that involves touching the participants (such as accommodating the adolescent in the scanner). We will wipe all instruments, scanners, and surfaces that the adolescent, their parents, and staff may encounter with disinfectant wipes provided by the CMRR or purchased by our study. **Meeting in person is necessary for the 2 neurofeedback training days**. Additionally, we will make every possible effort to call the participants at least 24 hours in advance so that we can screen them and their caregivers before any in-person appointment. Similarly, if any of the staff is known to be sick or potentially showing signs of illness, we will relieve that staff from face to face contact and take protective measures for the remaining personnel outlined by University of Minnesota's Office of the Vice President of Research's 'Covid-19 Guidance for the Research Community'(https://research.umn.edu/covid-19-guidance-research/overview). All staff that will be engaging in face-to-face contact with participants will be encouraged to vaccinate when vaccines are available.

Risks related to MRI

a. *Claustrophobia.* If participants become uncomfortable, they will be given the option of discontinuing the study. No medications (e.g., benzodiazepines or tranquilizers) will be offered to them. The PI and/or MRI trained research staff will be present throughout the experiment and will be on hand to talk to the participants and ensure their comfort.

b. *Magnetic pull-on metal objects.* Individuals with implanted metallic foreign bodies will be excluded.

c. *Scanner noise.* Participants will be given sound-reducing insert plugs to wear during the scan to diminish any discomfort due to noise and to protect their hearing. A microphone and emergency signal will be provided so that they may stop the testing if they become uncomfortable or anxious at any time.

d. *Mild symptoms.* If the participant notifies the researcher of pain or discomfort, they will be removed from the scanner.

e. *Boredom*. Participants will view scenes from a nature movie while structural images are collected to help ease boredom during the scan.

f. *Potential for discovery of brain abnormalities.* We will refer participants to their provider and share the information from the study as indicated and if requested by the participant. Specifically, will refer the family to a radiologist (covered by the family's insurance) and provide them with a copy of the structural images if so desired.

g. Energy from the scanner can cause heating or nerve stimulation. We will ask participants to remove all jewelry before the scan. For participants that have metal on the body that cannot be removed, we will review this carefully, and exclude participants as indicated. We will teach participants that if they feel any tingling or unusual sensations during the scan, or muscle contractions, they should use the squeeze bulb to alert the researcher immediately.

Note: We will use the existing screening form (CMRR Subject Safety Screening Form) already in place at the CMRR which has IRB approval to screen for the above risks related to MRI.

New psychiatric disorders. If during the screening procedures, criteria are met for a psychiatric disorder that is not currently being treated, a referral for appropriate treatment will be offered if desired by the participant and/or the parent. Referrals will be made to the

UMN Department of Psychiatry Child and Adolescent Clinic, or other appropriate sites, as determined by the PI, who is familiar with mental health resources in the community. A protection safety plan will also be a part of in-person or phone evaluations.

Medication related issues. All participants will be referred to their psychiatrist or nurse health practitioner to manage medication issues. If medication related issues are reported and the family/participants lacks a psychiatrist or health practitioner to consult with, we will refer the caregivers/participants to the University of Minnesota outpatient psychiatric clinic for a consultation with a providing pediatric psychiatrist or to expedite services with a licensed nurse practitioner if the family chooses to do so.

16.8 **Reproduction Risks**: It is unknown whether exposure to magnetic fields affects embryos or fetus. Pregnant participants may be excluded.

16.9 Risks to Others: N/A

17. Potential Benefits to Participants

17.1 **Potential Benefits:** There is no guarantee of benefits. Active amygdala versus placebo neurofeedback has been associated with reduced depression and anxiety, reduced emotion dysregulation and dissociation among adult patients with depression and borderline personality disorder [32,34,35,43,53,54]. These are two conditions linked to suicide attempts risks, so ***if*** the proposed treatment is effective there is a significant potential for benefits to the participants. Both depression and borderline personality disorders are associated with suicide attempts. The effects of active neurofeedback have been reported to last up to 2 months after the intervention with the slope of symptom reduction accelerating as time passes in comparison with placebo neurofeedback.

18. Statistical Considerations

Data Analysis Plan. SPM12 [55] will be used for fMRI statistical analyses. EPI time series' preprocessing will include: (1) realignment for motion correction, (2) slice timing correction, (3) co-registration of EPI with anatomical data, (4) spatial normalization to MNI anatomical, and (5) spatial smoothing. Head motion outliers in EPI time series will be corrected using the Artifact Detection Tools with a scan-to-scan movement threshold of 0.2 mm and a scan-to-scan global signal change of 3 SD [56]. Activity. For each subject, BOLD activity contrast signal variance will be modeled with regressors using a General Linear Model (GLM) to generate 1st level contrasts (NF vs. CB and NF vs. Rest) for the ESF-NF task similar to procedures followed by Young et al. [32]. Dr. Karina Quevedo will lead activity analyses. Connectivity. Time series in dACC or right-amygdala for the ESOM and ER tasks will be used to yield general psychophysiological interaction (gPPI) contrast variables [57]. The gPPI variables represent FC differences for 'self' vs. 'other' faces recognition or 'regulation' vs. 'passive' viewing. The processing pipeline configuration will be available online. The research staff and a software programmer will generate automatic pre-processing scripts using pilot adult data to yield 1st level images for both activity, connectivity, and structural data to ensure rapid quality control and data access. General PPI analyses yield information flow between neural nodes without direction of exchange. Competing models of affect valuation versus affect modulation/suppression assume 'bottom-up' influence from amygdala on mPFC or 'top-down' influence from the mPFC and dACC on the amygdala, respectively[58]. Dynamic causal modeling (DCM)[59-61] will follow up gPPI analyses to test bottom-up vs. top-down models of information flow between target neural hubs. DCM will also test FC patterns during NF training but increase target activity during NF is the key target for our Milestone 1. Dr. Paret will conduct FC analyses and determine how functional neuro-architecture of affect regulation and self-processing changes after NF training. Defining ROIs. In line with our focus on amygdala, dACC, and their connectivity with mPFC, we will target the dACC (MNI: x=-8, y=30, x=30), the highest loci of activity within the ACC in our pilot results and the right amygdala (MNI x=28 y=0 z=-19), the loci of our amygdala-ACC FC results in attempting participants [41]. ROIs of activity (5 mm) centered in those coordinates during NF, and their FC to mPFC (polar aspects of BA10-9) during ER and ESOM tasks are the target ROIs. The unrelated locus is the left horizontal segment of the intraparietal sulcus (MNI x=-42 y=-48 z=48). This region is not involved in emotion regulation or self-processing and has been used before as a locus of Unrelated comparison NF [32,34-36]. Finally, our decision of using specific coordinates, instead of localizing ROIs with a task that elicits dACC or amygdala activity, is supported using pre-determined coordinates for NF in research that yielded ROI up-regulation and symptoms improvement [32,34-36]. Accordingly, we have selected coordinates based on our published and pilot work. Puberty [51], illness or depression (BDI) severity, treatment indexes, substance use, IQ, handedness, or any variable differing between key groups will be covariates in all analyses.

Power Analysis: Power and R61 Milestones. With N=40 (20 per NF's loci), the R61 phase yields 80% power to detect an effect size of d=0.49 for one of the loci. Our data yielded statistically significant effect sizes of dAmygdala=0.37 and ddACC=0.324 in activity increases during a short version of the proposed ESF-NF task. Longer NF duration yield effect sizes as large as d= 1.2 as shown by Young et al. [32,34-36]. Since we focus on target circuitry identified by prior studies, we will employ region of interest (ROI) for connectivity and activity analyses in the R61 phase.

Statistical Analysis: Milestone (1-2) tests: Neural targets' activity (dACC or Amygdala) during NF will be tested using 1st-level NF vs. CB similar to Zotev et al. [36] and NF vs. Rest , similar to Young et al. [32,34-36] in single-sample t-tests (p-corrected, 0.01 using the AFNI program 3dClustSim voxel-level threshold of $p<0.001$) to identify regional effects controlling for key covariates noted in C3.2 for the ROIs and to estimate effect sizes during the ESF-NF task. Tests proposed for the ESF-NF task will be also conducted with the baseline and transfer runs to establish baseline (pre-NF) and post-treatment engagement of the neural targets. Neural targets' connectivity after NF. NF training effects in self-processing and affect regulation neural circuits during the ESOM and ER tasks, will

be performed on 1st-level gPPI contrast images [62] representing FC estimates for 'self' vs. 'other' faces recognition and for 'regulate' vs. 'passive' viewing conditions (with similar thresholds as above). Right-amygdala or dACC to mPFC FC will be tested with 1st level gPPI maps in mixed-effects analysis-of-variance (ANOVA) with time as within-group effects (Pre- and Post-NF training) to model FC parameters and compute effect sizes [57]. In a follow-up DCM analyses we will test for direction of information flow between hubs identified with gPPI analyses. Models for all plausible configurations of causal information exchange between two neural nodes (amygdala or dACC and mPFC) will be defined. The ESOM and ER task conditions are assumed to drive causal information flow. Links with psychological targets: Amygdala and dACC to mPFC FC will be extracted and correlated with changes in psychological targets, i.e., emotion regulation and self-processing behavior in the ETB [40] and IAT [38,39] before vs. after NF training. We will also test correlations with self-reported change (DERS, SPPA, RD) in those constructs [23-25].

R33 Aim 1: Confirm target engagement in the NF versus the Unrelated-NF group.
H1.1: Right amygdala or dACC activity will be higher for active versus unrelated-NF. A Bayesian ANOVA model will be fit for each ROI, where the primary predictor for each model is the indicator for the NF group, which will quantify the difference in activity parameters between the NF and Unrelated-NF groups.
H1.2: Right amygdala or dACC – mPFC FC will be higher during self-processing and affect regulation tasks following active NF compared to Unrelated-NF training sessions. A Bayesian analysis-of-covariance (ANCOVA) will model how each of the FC parameters relate to each of the affect dysregulation and self-processing behavioral scores. The predictors will be the NF indicator terms, which will quantify how each of these scores are affected by NF, the main effect of the neural target, and the interaction term between main effect and NF indicator. This interaction term will measure the difference in the association between the neural targets and the behavioral scores between the NF and Unrelated-NF groups.

R33 Aim 2: Test the relationship between neuropsychological targets' engagement and behavioral changes.
H2.1: Lower affect dysregulation and abnormal self-processing behavior will follow active compared to Unrelated-NF, mediated by amygdala or dACC to mPFC FC changes in self-processing and affect regulation tasks. Bayesian mediation models will test the role of dACC or amygdala-mPFC FC changes on the relationship between NF and affect dysregulation and self-processing behaviors (ETB and IAT) [63]. The outcome will be the behavioral change (ETB, IAT). The 1st linear model will be one used for H1.2, to test the relationship between the change in FC parameters and behaviors. For the 2nd linear model, the primary predictor will be the indicator term for the NF group, to establish the relationship between NF and behavioral change. Finally, in a 3rd model, the primary predictors will be indicator terms for the NF group, the change in FC parameters, and the interaction between them, to quantify the degree to which NF modifies the relationship between the change in FC parameters and behavioral change.
H2.2: Higher amygdala or dACC to mPFC FC after NF will be associated to lower suicide ideation. Bayesian linear model will use suicide ideation as the outcome, (C-SSRS, SIQ scores) and change in dACC or Amygdala-mPFC FC parameters in the ESOM and the ER tasks as the primary predictors.
H2.3: Affect dysregulation or abnormal self-processing behavioral changes will mediate the association between changes in FC and suicide ideation changes after versus before NF. Bayesian mediation models will test the direct and indirect effect of NF on suicide ideation, but this time we have two mediators: the neural targets and affect dysregulation or abnormal self-processing behavioral scores (ETB and IAT) [63,64]. These mediators will interact, as we proposed in H2.1. We will fit a Bayesian mediation model with multiple mediators but this time with suicide ideation as the primary outcome, to quantify the direct and indirect effects of NF on suicide ideation change, with each of the change in FC parameters, affect regulation and self-processing behavior as potential mediators. We will fit another model that contains these mediation models as sub-models, i.e., a linear model with the NF indicator as primary predictor, each of the main effects for the change in FC and behavioral change, and an interaction term between the change in FC parameters and behavioral change.

Bayesian Analyses in the R33 phase will use weakly informative priors using effects reported in the literature. Priors are a key strength of Bayesian models as they allow use 0f prior information to regularize models, e.g., using R61 phase results to adjust models in the R33 phase. This will boost statistical power since data from both phases will be used. Posterior distributions for model parameters will be constructed by combining priors with the likelihood function from the data. Markov Chain Monte Carlo (MCMC) procedures will be used to obtain samples from the posterior distributions for statistical inference. The Bayesian estimation will be implemented using custom R code in addition to the R package "BEST v0.4.0"[65,66].

Model selection and performance. In each of the Aims, we will start with baseline statistical model described above and improve the model by considering potential covariates that will allow the model to fit the data better and improve interpretability and predictive power. We will conduct a thorough search of potential statistical models that might improve on each of our baseline models. We will use residual analyses to assess how well each model fits the data and compute Bayes Factors to quantify quality of statistical models and use predictive cross-validation to assess the predictive capability of each model.

Data Integrity: The key scientific premise of this proposal is that improvement in emotion regulation and self-processing entail quantifiable changes in dACC and amygdala circuits. This proposal is aligned with the 2019 NIMH Strategic Plan 3.2: Develop ways to tailor new interventions to optimize outcomes and responds to the RFA MH-18-704: Development of Psychosocial Therapeutic and Preventive Interventions for Mental Disorders. Rigorous elements of the experimental design include: (**a**) using a specific threshold of

suicide ideation on psychometrically valid instruments (SIQ, C-SSRS); (**b**) random assignment, in the R33 phase, to active NF or to a Unrelated area NF condition; (**c**) use of HCP Lifespan imaging parameters on a Siemens 3.0 Tesla Prisma scanner, currently the best platform for high-resolution brain imaging; and (**d**) making all data and analytic algorithms available on a yearly basis for ready access by the wider scientific community using the GitHub platform. Full access to all data is the best means of assuring rigor and reproducibility; (**e**) although MDD and PTSD disorders afflict females more frequently than males, we intend to enroll both genders to explore the effect of biological variables on responses to NF training.

19. Health Information and Privacy Compliance

19.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ **I am requesting that all research participants sign an approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).**

This will include HIV/AIDS, genetic testing, mental health diagnosis/treatment records, drug & alcohol abuse or sickle cell anemia status of the offspring/participants participating in research because these conditions/statuses can affect brain function and intellectual achievement in IQ tests, and we need to control for them.

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g., Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

19.2 **Identify the source of Private Health Information you will be using for your research (Check all that apply)**

☒ **I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me**

☒ **I will collect information directly from research participants.**

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ **The PI, a licensed clinical psychologist with access to EPIC (an electronic record system) will pull records directly from EPIC or request them from another mental health facility or from another EPIC provider, only <u>after</u> participants provide permission and sign an approved HIPAA Disclosure Authorization to participate in the research (either the stand alone form or the combined consent and HIPAA Authorization).**

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☒ Other. **Describe: With the participant's express permission via a standalone form or the combined consent and HIPAA Authorization the PI and the research staff may access the EPIC inpatient records for a participant/family/consenting legal guardian that has provided the appropriate permissions to do so. Additionally, with the express authorization of the participant and their legal guardian we will contact providers external to the University of Minnesota that are currently or have been caring for the participant and their families.**

19.3 **Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.**

Legal guardians, adult caregivers and participants will provide a release of information (patients will fill out their clinics standard form to be submitted to ETHOS).and sign the approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization). **Thus, only records from participants who have provided their consent will be accessed**.

19.4 Approximate number of records required for review: ~ **<u>300</u>**.

19.5 **Please describe how you will communicate with research participants during this research. Check all applicable boxes**

☐ This research involves record review only. There will be no communication with research participants.

☒ Communication with research participants will take place during treatment. Clinicians or research staff will extend permission to contact forms to reach out suitable participants and/or their parents so that researcher staff can contact the family and provide detailed information about the research opportunity.
☒ Communication with research participants will also take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We will communicate with participants verbally over the phone, via texts and emails (primarily for scheduling purposes), and in person. However, participants and their families may receive copies of the consent and assent forms in advance of their first session via email if they want to see the forms in advance. Email and texts will be also used primarily to confirm appointment times and dates and for participants to cancel if they wish to. Any time before or after consent and assent are signed, participants will have the option to sign a written authorization for text and email (in a form approved by **HIPCO**). For example, to permit the use of unencrypted emails for more detailed communication of information if they wish it about their research participation such as communication about eligibility and health information. This will also allow participants to receive an email with a summary of key findings after signing consent and assent form

19.6 Explain how the research team has legitimate access to patients/potential participants:

The research team will be permitted to access healthcare records with a completed **HIPAA** form. The data derived from the healthcare records are for the purpose of obtaining details about frequency and or history of prior hospitalization, prior diagnoses, presence of prior suicide attempts, and current or past medication. Data derived from the healthcare records could include reported instances of abuse that might not have been disclosed to the research staff and/or clinical history characteristics that investigators might have run out of time to collect or inquire about during the first visit.

19.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☒ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In **REDCap** (recap.ahc.umn.edu) – This is a possible alternative though currently we might continue using simple password protected excel databases given that they are easier to format in data analysis friendly sets and REDCap can be difficult to transfer to readily usable data sets for analyses. Password protected excel databases will be kept in the ACH server and/or on Box.

☒ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

Path: Psychiatry: \\psych.ahc.umn.edu\psych)(N) or (\\ad.ahc.umn.edu)(S:)\Psychiatry_Share\Psych

Location of server: Department of Psychiatry University of Minnesota

IT Support Contact: Marcus Johnson, joh04270@umn.edu

☒ Store ☒ Analyze ☒ Share

☒ In an AHC-IS supported desktop or laptop with personalized access to the PI's google drive which is only accessible with the PI's password or express permission to access. Only completely **de-identified databases** will be kept on the PIs google drive.

Provide UMN device numbers of all devices:

20121593

20131013

20130021

20210910

20210913

Four new computers will be purchased and encrypted by the IT support of the AHC. Additional device numbers will be submitted to the IRB during routine annual reviews.

☒ Store ☒ Analyze ☒ Share

☐ Other. Describe:

Completely de-identified data sets will be kept in the PI University of Minnesota Google Drive and only those granted access by the PI will have access to it.

Indicate if data will be collected, downloaded, accessed, shared, or stored using a server, desktop, laptop, external drive, or mobile device (including a tablet computer such as an iPad or a smart form (iPhone or Android devices) that you have not already identified in the preceding questions.

☐I will use a server not previously listed to collect/download research data

☒ We will use a University secure desktop or laptop not previously listed to analyze and **store completely de-identified databases.** These databases will be purged of **all** participant's identifying information from the beginning. An age-calculator will be used to de-identify participants' date of birth while still maintaining an accurate age (in terms of months and years) for all collection points. We must include age in all analysis to control for developmental differences in brain maturation, thus de-identified age at each sampling point must be included in all databases and analysis.

☒ I will use external hard drives or USB drives ("flash" or "thumb" drives) not previously listed to analyze and store completely de-identified data bases. These databases will be purged of participant's identifying information from the beginning; they will be completely de-identified and contain no participant PHI. To track participants' age in a de-identified manner, an age calculator will be used to create a transformed date of birth (ex. with a randomly generated jittering number that shifts the date of birth -/+6 months).

☒ I will use a mobile device such as a tablet or smartphone not previously listed to analyze and store completely de-identified databases. These databases will be purged of all participant's identifying information from the beginning. All databases will be completely de-identified which means all databases will lack all participants' PHI and contact information.

Please note that in the above devices (tablet, smartphone, laptops) ONLY completely de-identified will be kept within the PI's Google drive which is only accessible with the PI's password and/or expressed access granted by the PI. **It is not possible to analyze, depict or work with the data without having de-identified databases that are shared with students or collaborators**.

Consultants. Vendors. Third Parties. Completely de-identified databases will be stored, shared, and analyzed within the PI Google drive application, which currently has a University of Minnesota license and has no limits in data storage. The data to store, analyze and share will be de-identified of all PHI. AHC supported tablets will be used to answer questionnaires during the clinical evaluation and behavioral session to help minimize time used for data entry. These databases will be purged of participant's identifying information, from the beginning they will be de-identified databases which will lack all participant PHI except for their date of birth.

19.8 Links to identifiable data: Numbers will link data to participant's information in an excel, passworded document kept in the AHC secure server or Box secure storage (See information above). The excel document containing the links between the numbers and the participant's information will be destroyed after key publications of the study pertaining to the identified principal outcomes are concluded.

19.9 Sharing of Data with Research Team Members. Completely de-identified data sets will be shared via the Google drive cloud platform (shared by the P.I.) and via the Minnesota SuperComputing Institute (MSI) a passworded secure data repository.

19.10 Storage and Disposal of Paper Documents: Any paper documents generated as a result of this research project will be kept in a closed room with a numeric code password. They will be disposed of after all the publications have been disseminated.

20. Confidentiality

Data Security: A numeric subject **ID** will be assigned to each subject. All samples, images, digital records, and forms will be marked with this numeric subject **ID** instead of the participant's identifying information. The direct identifiers that are maintained are either kept in locked file cabinets in locked rooms with controlled access, on Box Secure Storage, or on a secure password-protected

database with controlled access in the secure psychiatry server. No one except the research team will have access to the PHI files. The link between the identifiers and the subject ID will be maintained through a secure subject database and in a secure **AHC** server.

A password protected database of the participant's facial pictures and linking their identifying information to their **ID** numbers will be kept in a secure **AHC** server or Box Secure Storage at the department of psychiatry. Direct identifiers will be necessary to maintain contact with the participant in order to schedule appointments and follow-ups. Specifically, the subject's full name, date of birth, race and ethnicity, address, phone numbers and emails will be kept in our secured subject database in a secure **AHC** psychiatry server. This is necessary so we can make sure we are not asking for consent from the same person more than once for the same study. Video of the assessments will be recorded for scoring purposes and kept in a secure AHC server or in a secure physical location. Specifically, **CD's** or **external drives** will be kept in a locked room at the Department of Psychiatry. Pictures of the subject are taken to be used during the MRI task and are also kept in the secure psychiatry or **AHC** server. Members of the research team will be the only ones to view pictures and videos. Pictures of the subjects may be used during the **MRI** ESOM and neurofeedback tasks for future participants and research, if the participants provide approval in the consent and assent forms. **Electronic records** will be kept in password protected computers, drives, servers and/or e-documents. Additionally, written, or digital protocols/instruments/tasks will be identified with the participant's number and no identifying information will be kept in written or protocols/instruments/tasks. Participants will be advised that there will be limits to their confidentiality and that if suicide attempts immediate risks are suspected, or if child abuse or of vulnerable adults or risks of homicide are discovered there would be a need to contact the appropriate organizations and that their parents would be informed.

21. Provisions to Monitor the Data to Ensure the Safety of Participants

21.1 Data Integrity Monitoring

Data Safety and Monitoring Plan. Data management will be overseen by the PI. The personal health information data (such as faces and the links between the participants **ID** and their identifying information) will be stored at UMN department of psychiatry academic health center (**AHC**) secure server and only the study staff will have access to the server. Training: The PI will directly train the study staff in issues of maintaining data integrity and confidentiality. The PI will stress the critical importance of subject confidentiality in the training of all project staff and will keep reiterating this point as opportunities arise in handling such material. All data collection and storage will use the following safeguards to protect data integrity and subject confidentiality. All members of the project will have received human subjects training and certification through the Collaborative Institutional Training Initiative (**CITI**) curriculum. Data from interviews and questionnaires will be collected by members of the clinical assessment team.
The project manager or the experimenter in charge of the interview/procedure will be responsible for immediate transfer of the data from any temporary device or study device (if remotely taping interviews/conducting research procedures) to the secure storage areas/DVDs, AHC-supported server, Box Secure Storage, or external drives, and of deleting the data from any temporary devices, and of entering or transporting the data to a secure on-line database or locked room. All data will be de-identified and labeled only by participant **ID** numbers. These de-identified databases will be stored separately from the identifying personal health information and from signed consent and assent forms.
De-identified databases will be kept in the PI's passworded google drive (the PI will grant access to Investigators and the PI, or the project manager will remove them when they no longer work on the project). De-identified and ID coded information will be kept in the Minnesota Super-Computing Institute (**MSI**) or at the center for magnetic resonance research (**CMRR**) servers which are also secure passworded directories.

Data access will be limited to the Investigators and study staff who will receive human subjects training and certification through the **CITI** curriculum. Any staff member who has access to **PHI** data will receive training in the critical importance of subject confidentiality. Every effort, and ongoing adjustments, will be made to ensure that the identity of subjects will not be able to be determined using the data. Future use of the data includes research, demonstration, publication, public performance, and archiving. Subjects' permission for further use of their data, in de-identified form, will be obtained with the initial consent form. Data will be presented in aggregate form with identifiers removed. Drs. Quevedo, and the identified statistical consultants or CoI's will assume responsibility for statistical design and analysis of the study data and a software programmer will aid in the formatting and management of the databases.

The PI's monitoring of data will be ongoing throughout the project. The clinical assessment team will collect information regarding symptom severity, adverse events, and suicidality during the clinical visits. Any adverse events or concrete and impending plans for suicide attempts that is reported during these sessions will be documented and reported to the PI (Dr. Quevedo) to determine the next steps (such as referral to the emergency room for further evaluation in the case of severe adverse events or imminent suicide risk evidenced by concrete suicide ideation with a specific plan and time frame added to inability to provide assurances not to attempt suicide). **Note that the population to be recruited is required to have significant levels of suicide ideation, hospitalizations, and suicide completions.**
Any unexpected adverse events, unexpected problems that involve risk to the participants or others, or breaches of confidentiality, will be documented and reported immediately to the PI, who will determine the next steps (such as reporting to the IRB, as indicated.) The PI will monitor all data and will be available to study staff.

CTSI Monitoring: All regulatory and participant research files will undergo monitoring by University of Minnesota Clinical Translational Science Institute (**CTSI**) clinical research associates (**CRAs**) to assist investigators with regulatory compliance. CRAs

will also ensure that the study is conducted in accordance with the protocol and inclusion/exclusion criteria as approved by the IRB. Monitors review study materials (documents, records, drug/device accountability, Case Report Forms, etc.) to assure that the study is conducted, recorded, and reported in compliance with FDA Good Clinical Practice. Their goal is to partner with investigators to promote and facilitate compliance with Good Clinical Practice through: regular monitoring visits; quality assurance; data query resolution; review of study regulatory files; Adverse Event/Serious Adverse Event (**AE/SAE**) reviews; compliance consultation services; signed informed consent/HIPAA documents; Case Report Forms (**CRFs**); Medical records (for AE/SAE); regulatory binders; communications with FDA/IRB; and Investigational Product (IP) distribution logs.
The principal investigator and the research staff will work closely with the Clinical and Translational Science Institute (**CTSI**) monitor who will be working within the Department of Psychiatry to ensure that all documentation is up to Good Clinical Practices standards. The principal investigator and study staff will meet with the CTSI monitor prior to beginning the study to ensure that the protocol and regulatory binder are set up properly and regularly updated thereafter to ensure that study procedures meet regulatory standards. Further, research staff will submit safety and compliance reports to the monitor quarterly. Annual reports will be made to the IRB in accordance with its policies. The types of information monitored by the **CTSI** monitors will include demographic variables (including comorbid conditions), number of patients screened and reasons for exclusion, recruitment data, data quality, and baseline and follow-up data. Data on dropouts with reasons for early termination will be included, as well as data on assessment and visit compliance, and all adverse events, including those associated with study withdrawals. Any reports of adverse events will be made available to the CTSI study monitor, the local IRB, and the NIMH. The principal investigator or an authorized study coordinator (after consulting with the PI) will do the initial reporting of adverse events. Any serious adverse event, defined as "any untoward occurrence that results in death, is life threatening, requires inpatient hospitalization, or creates persistent, or significant disability" will be reported to the IRB and CTSI monitor. **Note that the population targeted by this study (Participants and/or patients who have attempted suicide) have a higher likelihood of a second suicide attempt, suicide completions and/or further hospitalizations. Thus, it is likely that AE or SAE will be reported for the proposed research that are not due to the research procedures but a characteristic of the population.** However, in compliance with the NIMH and U of M IRB recommendations, all AE and SAE will be reported regardless of whether they can be linked to research participation or not.

Data Collection. Participants will complete study procedures in several appointments in person or **via remote research**. During these sessions, the subjects will be closely monitored by study staff for any indication of compromised safety for the subject (See Figure 1). Participants will also be monitored for whether they are putting effort into study procedures. Following each session, participants will complete a brief volunteer online survey regarding their experience including any discomfort during the session or any mood or behavior change since their last session. Study staff will review these and notify the PIs if there are any concerning developments. The PIs and the IMM, with the possible alternative of the pediatric psychiatrist, will review the information gathered during in-person or via remote research assessments and determine if further evaluation or action needs to be taken. Participants will complete study procedures in several appointments/remote visits. After data collection occurs, data will be reviewed for accuracy and completeness by the individual who gathered the data or by a similarly trained staff member or student. After data are processed and entered, they will be reviewed statistically to ensure errant outliers are minimized. Data will be captured both electronically and in paper formats and in whatever format facilitates coding reliability, training, and consistency across personnel.

We plan to manage data in the following manner for all participants recruited from University of Minnesota sources. Each participant will be assigned a random, unique identification number. This ID number will be used on all files throughout the database. The participant identification number, rather than participant names, will be placed on all forms to preserve confidentiality. The forms will be reviewed for completeness and accuracy prior to data entry. The data entry modules will be designed to accept only the valid range of values for each variable to reduce risk of the entry of erroneous values. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, the University of Minnesota will take steps allowable by law to protect the privacy of personal information.

Data Sharing Plan. The PI will make data available to the general scientific community at the conclusion of the study. Given the fact that the entities involved in this application must be HIPAA compliant, de-identification of the data along HIPAA guidelines will guide the development of the final database to be shared. Information should be available to other researchers within 12 months of the conclusion of the study. Since methods of data sharing are just now being developed, it is certainly possible we will have to amend our original plan. However, our current plan would be to have the dataset available via the web through postings of the information on GitHUB. Data will be provided in several "user friendly" statistical formats, including SAS and SPSS. We will also provide a detailed protocol describing study methodology, and a code book describing all data elements in as much detail as possible. The availability of the de-identified data at these web pages would be announced in various journals and publications of interest to clinicians and researchers. In addition to shared information via GitHUB, we will share our data via the National Database for Clinical Trials related to Mental Illness (NDCT; http://ndct.nimh.nih.gov/; NOT-MH-14-015 and NOT-MH-15-012). Submission of descriptive data will take place annually (with the year count starting from first date of recruitment of the 1st participant) for the R61 phase given delays due to the COVID-19 pandemic. If the project moves to the R33 phase, data will be submitted bi-annually starting on the second year

of the R33 phase. Submission of all other data is expected at the time of publication, or prior to the end of the grant, whichever occurs first. Raw brain activity including EPI's and T1 images will not be uploaded without removing first all ways of re-constructing participant's faces (de-sculling and removal of soft tissue). Data that has undergone pre-processing may be uploaded. We will share results, positive and negative, specific to the cohorts and outcome measures studied by using the study functionality (see http://ndct.nimh.nih.gov/results).

As part of the data sharing, participants and their caregivers will receive periodical updates on any preliminary results as well as milestones achievements as needed. We will also share results via social media such as Facebook and twitter and email participants about posters or publications of the data.

Data and Safety Monitoring Board. The PI will convene a Data and Safety Monitoring Board (**DSMB**) once a year (or ad-hoc depending on if conflicts of interests suddenly emerge). During the yearly meeting they will review AE or SAE that emerge. The DSMB includes a biostatistician, a researcher with expertise in adolescent self-injury, and a clinical psychologist. They will meet annually to 1) monitor the safety, quality and conduct of this study and 2) decide whether adequate subject safeguards are in place. The DSMB will review: 1) the progress of the proposed study, including assessments of data quality and participant recruitment, accrual and retention; 2) outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue, be changed, or terminated; 3) external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study; and 4) study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data. **Note that the population targeted by this study (Participants and/or patients who have attempted suicide) have a higher likelihood of a second suicide attempt, suicide completions and/or further hospitalizations. Thus, it is likely that AE or SAE will be reported for the proposed research that are not due to the research procedures but a characteristic of the population.**

The study biostatistician will be responsible for generating a de-identified annual report of key events that will be reviewed as part of the safety monitoring of the protocol. The tentative list of key events will include and more specifically: 1) unexpected side effects to the study treatment, 2) suicide attempts, 3) hospitalization, 4) worsening in non-suicidal self-injurious behaviors (e.g., acute worsening in frequency or severity of injuries), 5) premature drop-out from their standard of care treatment, 7) medication adherence, 8) suicide completions. These key events will be reviewed at the first meeting of the DSMB to obtain the DSMB members' input into the list and to add any other events or measures that they feel would be relevant to include for evaluating the safety and conduct of the clinical trial. **See the data safety and monitoring plan (DSMP) uploaded in the supporting document's section in ETHOS for IRB review.**

Definition of Events: a) Any serious adverse event, defined as "**any untoward occurrence that results in death, is life threatening, requires inpatient hospitalization, requires medical or surgical intervention, or creates persistent, or significant disability**" or unanticipated problems that are "unexpected, related or possibly related to participation in the research, and suggests that the research places the subjects at a greater risk of harm than was previously known or recognized". b) expected or unexpected adverse events, describes as "any unfavorable medical occurrence, including any abnormal sign, symptom, or disease, temporally associated with the subjects participation in the research, whether or not considered related to the subject's participation in the research"; there is a level of expected adverse events in all research (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AA**).**

Reporting. Any unexpected adverse events, and unexpected problems that involve risk to the participants or others, or breaches of confidentiality, will be documented as per indicated in the Good Clinical Practices Standards and reported by all research staff to the PI, who will determine the next steps including coordination of response with the IMM or the pediatric psychiatrist. After been informed by any study personnel or directly becoming aware of SAE's or AE's, the PI will report any unexpected serious adverse events (**SAEs**) or adverse events (**AE**s) or unanticipated problems (**UP**s) involving risks to participants to the IMM or the Pediatric Psychiatrist and work with either of them to determine its severity and attribution. After consulting with the IMM or the Pediatric Psychiatrist, with aid of study coordinators –SC-, the PI will email a signed form regarding the event to the **IRB** and to the assigned national institute of mental health (**NIMH**) program officer (PO), the **DSMB** with copy to the **IMM** regarding the AE or SAE. See **Figure 2** for the flow of information and decision making.

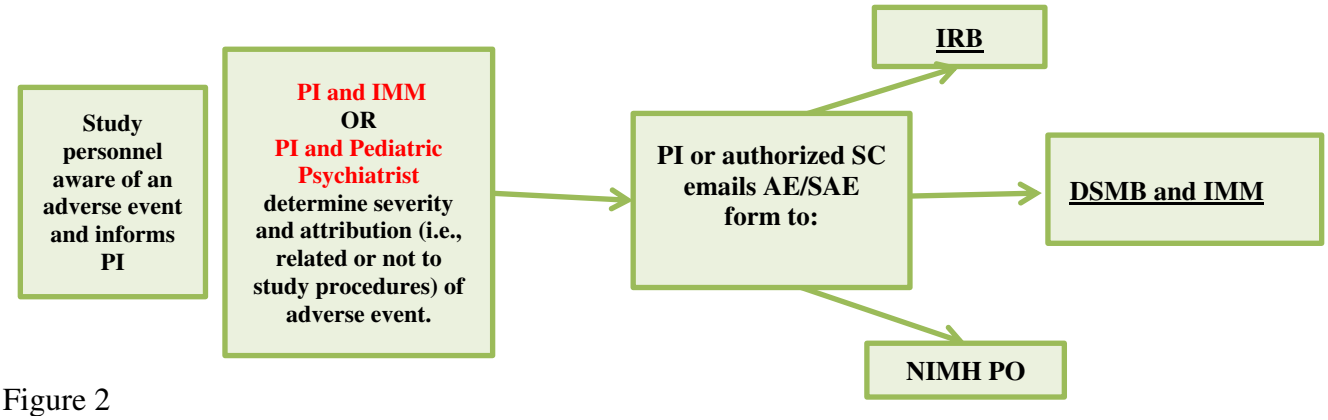


Figure 2

Documentation to be submitted for reportable events will include the following: 1) Brief identifying information for the research protocol, 2) the date or approximate timeframe that the event occurred on and the date the PI became aware of event, 3) a description of the event and impact to the participant, 4) a description of measures taken in response (if any), 5) Confirmation monitoring entities and regulatory bodies were notified as proposed, 6) Attribution of the event/events, specifically linked or not to study or protocol procedures, 7) a description of corrective actions and changes to the protocol that have either been made or proposed if the event can be reasonably attributed to protocol or study procedures.

If the CTSI monitor or the DSMB notes serious and unexpected adverse events, or unanticipated problems involving risks to participants or others that have not been reported by the PI, the PI and IRB will be notified. This will be done via a letter from the CTSI monitor or the DSMB Chair/Administrator to the PI for distribution to the institutional official, sponsor (PO), and IRB. The PI will also submit an annual progress report to the IRB summarizing the data and safety monitoring activities and outlining: 1) whether participants' safety, privacy and confidentiality has been consistently assured, 2) whether research instruments have been administered in a way that protects participants' privacy, 3) progress towards recruitment goals, quality of data collection (e.g., appropriate completion of forms), and participant retention/ attrition rates, and 4) a review of new scientific literature pertinent to the safety of participants or the ethics of research participation.
If the DSMB notes reported adverse events, serious and/or unexpected adverse events, or unanticipated problems involving risks to participants or others which appear to be **related** to the research procedures during study, the PI, PO, and IRB will be notified. This will be done via a letter from the DSMB Chair/Administrator to the PI for distribution to the institutional official, sponsor NIMH PO, and the IRB after the yearly meeting. A yearly report will be made to the Data and Safety Monitoring Board (DSMB; detailed above) including all SAEs and AEs

Timeframe for Reporting. The PI will report to the IRB and the assigned NIMH PO within the following timeframe: (1) **IRB/IMM/DSMB** suspensions or terminations (within **3 business days**), (2) deaths related to study participation (within **5 business days**), (3) unexpected serious adverse events (within **7 business days**) (https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml), (4) unanticipated problems involving risks to participants or others (within **10 business days**), (5) serious or continuing noncompliance (within **10 business days**), **(6) adverse events deemed expected or unrelated to the study (with annual progress report)**, and (7) protocol deviations that do not affect the scientific soundness of the research plans or the rights, safety or welfare of the human subjects (with annual progress report) (https://www.nimh.nih.gov/funding/clinical-research/nimh-reportable-events-policy.shtml).

ClinicalTrials.gov Requirements. The study will be registered with *ClinicalTrials.gov* prior to the enrollment of the first subject.

22. Provisions to Protect the Privacy Interests of Participants

Protecting Privacy: Each participant will be assigned a random, unique identification number. This ID number will be used on all files throughout the database. The participant identification number, rather than participant names, will be placed on all forms to preserve confidentiality. Data from interviews and questionnaires will be collected by members of the clinical assessment team. The project manager or research staff recording online interviews will be responsible for immediate transfer of the data from their temporary device or terminal or study device to the secure storage area, and of entering the data to a secure on-line database. All data will be identified and labeled only by participant ID numbers and will be stored separately from the identifying information and from consent and assent forms. Identifying personal information data such as faces and links between participant's ID's and their personal information will be kept on a secure server at the department of psychiatry at the UMN or a Box Secure Server created for the current study and only the study staff will have access to the server. De-identified data will be also stored at the Minnesota Super-Computing Institute (MSI) or in DVD's or external drives that will be kept in locked rooms in secure locations at the Department of Psychiatry. This includes video-

taped remote research or in-person sessions that were videotaped via Zoom, in person, or some other remote online platform. The PI will consult with MSI engineers to store videotapes of sessions with participants in MSI in the safest, most secure way possible.

Data access will be limited to the Investigators and study staff who will receive human participants training and certification through the CITI curriculum. Any staff member who has access to participants or data will receive training in the critical importance of participant confidentiality. Every effort, and ongoing adjustments, will be made to ensure that the identity of participants will not be able to be determined using the data. Future use of the data includes research, demonstration, publication, public performance, and archiving. Participants' permission for further use of their data, in de-identified form, will be obtained in the initial consent form. As stated, ID will link data to participant's personal health information in an excel, passworded document kept in the academic health center (AHC) secure server or Box secure storage. The excel document containing the links between the numbers and the participant's information will be destroyed after all publications of the study pertaining to the identified principal outcomes are concluded.

Participants will be assured that sensitive information about their relationship with their parents, their sexual orientation, sexual experiences, experimental drug use or other sensitive information will not be shared with their parents. However, both participants and parents will be advised that there will be exceptions in confidentiality that include new knowledge of abuse of vulnerable children or adults, impending and concrete risks of harm to self or others. Part of the interview entails describing instances, methods and emotions surrounding prior suicide attempts. Every effort will be made to convey the expertise and comfort of the research staff with this information and to acknowledge and validate any feelings of discomfort that such disclosure might elicit in the participant. Similarly, the interview entails disclosing past instances of exposure to abuse or maltreatment, and the staff will support participant's emotions or feelings during the interview, offer breaks, verbal comfort, and validation of their emotions. Participants will be encouraged to disclose information in their own time and to the extent that they feel comfortable with.

23. Access to Participants.

The research team will have access to the participants' information because the participants and their parents will sign a HIPPA form granting access to their medical records. The information that research staff may gather entails present and past diagnosis, present and past medications, present and past hospitalizations, and suicide attempts as well as reports of abuse recorded in their history.

24. Compensation for Research-Related Injury

24.1 Compensation for Research-Related Injury: The research does not involve greater than minimal risk in its procedures though it does involve a population at risk. Given that the neurofeedback and other procedures involved entail minimal risks there is no available compensation for research-related injuries.

24.2 Contract Language: Please see the consent and assent forms.

25. Consent Process

25.1 **Consent Process in person**:

Participants will be identified in a variety of ways including parent and adolescent filling permissions to contact, use of a Quick Response (QR) code indicating a permission to be contacted, ER staff, clinicians or doctors' referrals to research staff, and letters sent to the family of participants discharged from or currently receiving care at emergency room or in inpatient services. Parents and Participants will also contact the study via phone calls, brief texts, or emails.

To limit coercion, all referring adults that provide clinical services to a participant (clinicians, doctors, and ER personnel) as well as research staff will ensure that participants and their caregivers understand that: **1st their decision to participate or not does not affect the quality or availability of care. 2nd the permission to contact or Quick Response (QR) code prompt is <u>not</u> a formal consent document. 3rd Participants will be told that <u>only</u> their parents or designated adult caregivers can consent to participate in their behalf by signing a consent form.**

Research staff will call the family home and screen suitability for inclusion in research. This call is to establish suitability and agree on a meeting day. There are instances where the parents or legal guardians cannot attend the first research session due to illness, travel, work, or other circumstances. This is likely to occur in a research study that entails at least 5 visits.
There are also cultural differences in how Participants are taken care of, for example Latino and African American families often place Participants with an alternate caregiver such as a grandmother or aunt when there is a history of family conflict, difficulties with access to housing or the parents are not in the U.S. African American (AA) and Latino families often share caregiving responsibilities with extended family with participants placed with aunts, grandmothers, or older siblings while the legal caretakers are in their country of origin or temporarily not accessible. If biological/adoptive parents are not available to consent on the behalf of a minor, the study team will work with the Office of General Counsel to ensure appropriate legal authority to consent. In the case of a court appointed guardian, consent for the child can be given if the court first approves the experimental treatment or if the court's guardianship specifically authorized the guardian to consent to research participation. Recruitment of AA and Latinx participants to be represented in research is a priority of NIMH and a sorely needed effort in research. Acknowledging the cultural differences and the prevalence of non-nuclear

households in low SES and non-white populations would be of great benefit to families and Participants in need for this kind of research and treatment alternatives. **We are requesting that such family dynamics be taken on a case-by-case basis and necessary modifications and precautions—with consultation of the Office of General Counsel to ensure appropriate legal authority to consent—be allowed to minimize unduly exclusion of participants underrepresented in research.** ***If someone with authority to provide consent cannot be determined, the potential participant will not be enrolled.***

These accommodations are necessary because the population of suicide attempting Participants is already very small to begin with, accepting initial consent from adult caregivers is necessary to increase the ease to recruit participants that meet the strict criteria for this research. However, every effort will be taken to ensure that parents/legal guardians are the first signers of the consent form. During **Visit 1** experimenters will again explain the procedures and use the teach-back method to ascertain that the parents/caregivers and the adolescent understand the concept of research participation. The UBACC[67] will be directly completed by young adult participants' aged 18 years old.

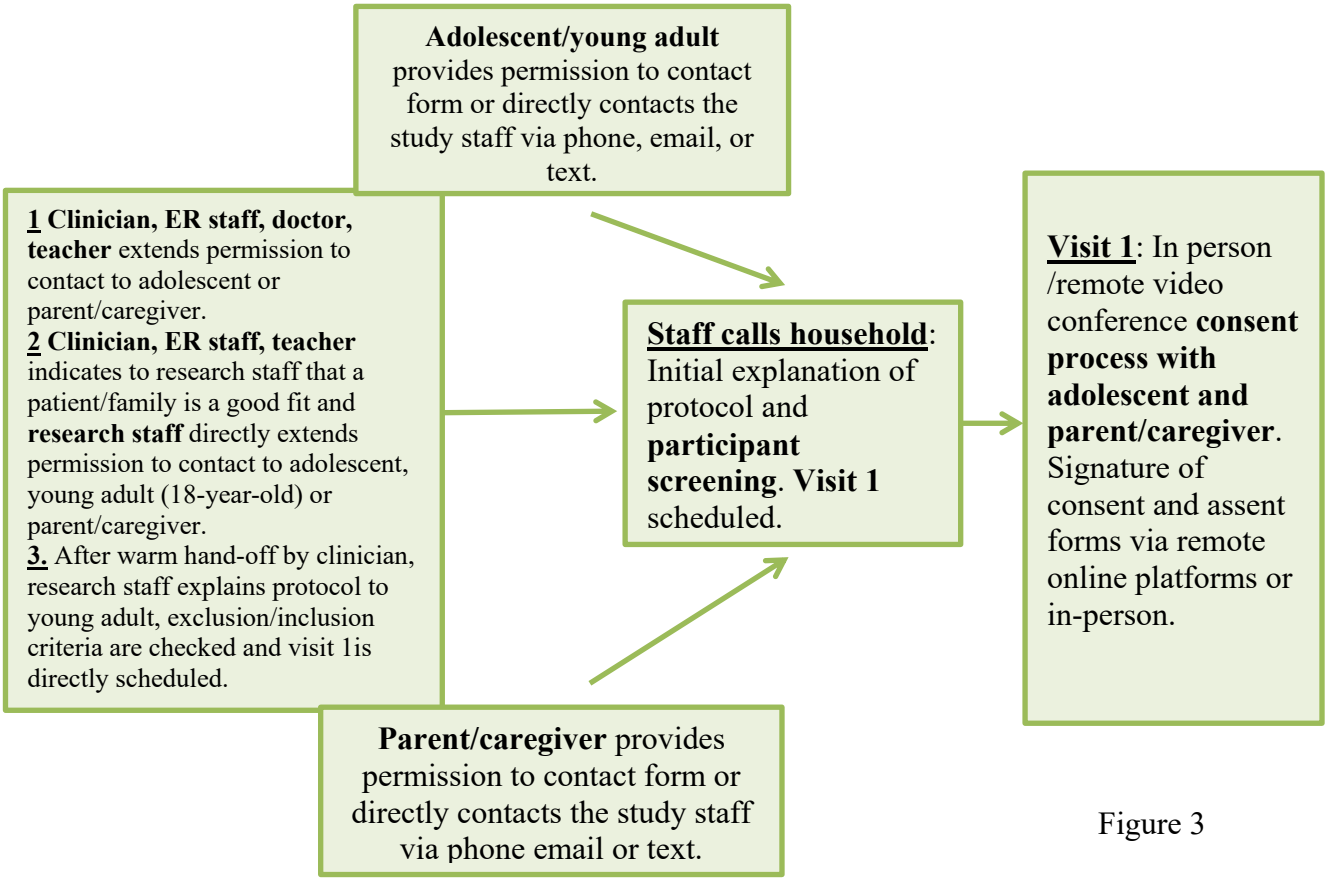


Figure 3

The purpose of **the call to the household** is to provide preliminary description of the study to both parents and participants and to establish suitability for study participation. **This call does not represent the final consent or recruitment procedure**. Is a preliminary step to establish suitability and agree on a meeting day. After establishing suitability for inclusion, the research staff and the family will agree on a date to conduct the **general procedures described in Table 1**. If the family agrees, a written electronic version of the consent and assent forms can be emailed to them in advance, or the family/caregivers/parents can communicate the consent and assent forms and the HIPPA form in some other modality. Before initiating any research procedures, during Visit 1 the acting experimenter will again explain the research procedures in detail and use the teach-back method to ascertain that the caregiver and the adolescent (or young adults) understand the concept of research participation [67]. After ascertaining understanding of- and capacity to consent to research procedures, parent/caregiver and research staff will sign consent forms and participants will sign assent forms.

Communications during consent process.

Participants and their parent will be able to call, text or email the research staff to express interest in participation using phone numbers such as (612-888-5669, 612-273-9761, 612-626-6952, 612-624-4245, 612-624-4223, 612-624-4410, 612-624-8088) or other

approved numbers by the department of psychiatry and the IRB. This will also entail the use of software applications (e.g., TigerConnect, Soft-Phone). Any modifications will be submitted to the IRB or/and consulted with our partners in CTSI. We are asking that phone numbers are entered at the time of signature of assent and consent forms to allow for this flexibility.

As part of the consent and assent process experimenters and authorized study staff conducting the consent and assent process, will write down fast mobile phone numbers (may be numbers approved by the department of psychiatry and the IRB and/or may entail the use of IRB compliant software (i.e. TigerConnect, Soft Phone)) so that enrolled parents and participants can quickly get in touch with the research team (to provide driving directions and fast contact information while enrolled in the study) by using their consent/assent documentation as a guide. For small logistic steps such as aiding with parking instructions and directions to buildings the research staff might use their personal phones and have the participant's number similarly assigned as "TBT-participant ID." No phone number will be identified with a participant's name, address, or any other kind of PHI in research staff phones. Even after these precautions, all call logs will be deleted. Because we will have several research assistants and personnel authorized to consent participants, we are requesting that the study staff name and phones associated with the study (e.g., 612-888-5669, 612-273-9761, 612-626-6952, 612-624-4245, 612-624-4223, 612-624-4410, 612-624-8088) are entered at the time of the consent/assent signature. Additional phone numbers will be submitted to CTSI and the IRB and/or to HIPCO for approval.

Upon consulting our data safety and monitoring board (DSMB), we were advised to provide cell phone numbers and ask the participants to program them with the **Teen Brain Training** name. The use of personal phones **in emergency situations** will follow the protocol delineated by the University of Minnesota (for example using re-dealer (612-336-2699) and deleting call logs etc.). The PI and those with the proper certifications and professional relationship with the University of Minnesota will follow similar protocol. The boxes in the consent and assent forms look as follows:

Researcher: Karina Quevedo, PhD, L.P. Department of Psychiatry Phone (mobile): _____ Phone (landline): 612-273-9761 business hours Email: queve001@umn.edu non-emergency, fast reply.	TBT Study Staff: _____ Phone (mobile): _____non-emergency fast reply. Phone (landline): (612)626 6952 business hours. Email: teenbraintrain@umn.edu non-emergency, fast reply.

25.2 **Consent process during remote research.**

The consent process via remote research will entail explaining the research (procedures, risks, and benefits) via a remote terminal using a remote calling/video platform that the participants and their caregivers agree to use (strong preference for **Zoom**). Parents and Participants will be in a video screen interview that will be hosted by the experimenter. These interviews will be recorded and saved by the experimenters in secure passworded servers, or virtual directories, or in external drives and DVD's that will be kept in locked archives and rooms. Prior to the day of the video conference interview, experimenters will email the consent, assent and the HIPPA forms to the parents and the Participants. Parent/caregiver and Participants will receive a HIPAA compliant link to sign consent, assent and HIPPA forms electronically on the day of the interview (for example RedCap or other equally supported software platforms). Videotaped remote 1st sessions or any videotaped session (for example, discussions of assent and consent) will be deleted from all unsafe locations, phones and email inboxes or trashes and saved in secure locations such as AHC servers, CMRR, MSI, secure locations, and/or DVD's or external drives that will be locked in a secure location at the Department of Psychiatry to which only staff personnel will have access.

25.3 Waiver or Alteration of Consent Process (when consent will not be obtained): NA.

25.4 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): We are applying for waver of documentation of consent for the screening phone call. We will use a phone script and will get a verbal agreement from the participant and/or their parents/caregivers before we proceed with screening questions (**See Attached Phone Screen**).

25.5 Non-English-Speaking Participants: Spanish speaking participants and families will be included in this research and consented initially with the short consent form method. As soon as possible the PI will translate and certify the full consent form. Spanish is the first language of Dr. Karina Quevedo who will conduct the research procedures in their entirety when Spanish speaking families are included in this research. To participate in the study Participants ought to speak English with reasonable fluency, but their parents/legal guardians can speak only Spanish.

25.6 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Date of birth as reported by both the caregiver and the adolescent will be used to determine legal age. In the case of participants who are younger than 18 years old, one parent (even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care

and custody of the child.), legal guardian or an authorized alternative caregiver (e.g. grandmother, grandfather, aunt or uncle) that shares the adolescent care and who has parental permission or temporary guardianship, may be able to provide consent. **In cases where the biological/adoptive parents are not available to consent, the study team will seek guidance from the office of general counsel to ensure caregiver has appropriate legal authority to consent. If someone with legal authority to provide consent cannot be established, the potential participant will not be enrolled**. The latter is a provision to ensure participation of participants whose parents are unable to attend due to a mutually agreed caregiving agreements to protect participants, or who may rely on extended family to care for their child and help them to participate in research. Participants will assent to participating in research by signing an assent form and their understanding of research procedures will be established via the teach-back method.

25.7 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: *N/A*

25.8 **Children/adolescent participants that become 18 years old during the study will sign a new adult consent form and the UBAC will be administered to establish capacity to consent.**

25.9 Adults Unable to Consent: NA

Adolescent participants aged 18+ that are not able to consent or that demonstrate lack of understanding of research via the UBACC will be excluded or staff will endeavor to correct their understanding of research versus clinical provision of services and other characteristics of research endeavors.

26. Setting

26.1 **Research Sites:**

Participants will be identified in in-patient units and emergency rooms around the Twin Cities, including those in the Fairview U of M Clinic. Research procedures will be conducted at the U of M center for magnetic resonance research (***CMRR***) and at the U of M department of psychiatry.

26.2 International Research:

- NA

27. Multi-Site Research

- NA

28. Coordinating Center Research

28.1 NA

29. Resources Available

29.1 Resources Available:

During the 2-year R61 phase, we anticipate screening ~120 participants using standard MRI eligibility questions and screening for suicide ideation and attempts. A minimum of 56 participants will undergo baseline tests and pre- NF training tasks over 2 years. Historically, we have obtained fMRI and structural data with stringent criteria of signal-to-noise ratio and movement (i.e., displacement <0.2 mm) in ~90 % of participants in the target age range and disorders. Some attrition is expected due to movement and treatment discontinuation. We anticipate garnering good quality scans for all NF sessions in ~50 participants over 2 years randomly assigned to dACC or Right-Amygdala NF-Training. We budgeted for additional repeat scans to recover lost data if needed. We expect that 40 participants will complete all post-NF assessments and 1-month follow-up assessment, yielding 20 data sets per NF target with high quality scans and pre and post NF training data in the R61 phase.

We anticipate screening ~290 contacts for MRI eligibility over 3 years in the R33 phase. We expect to perform 100 baseline evaluations and pre-treatment tasks and to garner ~90 high quality scans for all NF sessions randomly assigned to active (dACC or Right-Amygdala depending on research phase) versus Unrelated-NF. Of those we anticipate at least 72 will complete the post-NF training phenotyping and 1-month follow-up. We have budgeted for repeat scans per year to obtain 70 complete pre and post NF-training phenotypical data and high-quality NF scans.

The emergency department is within the same building where the research procedures will take place, so it will be extremely easy for research personnel to walk the family for an emergency assessment if suicide ideation reaches worrisome signs. Additionally, the PI, Dr. Quevedo will be able to provide clinical services to some participants if they wish to receive outpatient therapy after concluding the research study or after an impatient hospitalization.

To ensure that all people assisting with the research are adequately informed about the protocol the PI will personally train all research assistants and students aiding in data collection and involved in contact with participants. Additionally, all consultants, Co-I's and collaborators will receive a copy of the protocol and the IRB application before starting in the research.

Center for Magnetic Resonance Research (CMRR). The CMRR is located on the University of Minnesota campus at 2021 Sixth Street SE, Minneapolis, MN**,** 55455. This imaging center was established in 1991 because of the rapidly growing and successful in vivo magnetic resonance imaging (MRI). CMRR is an interdepartmental and interdisciplinary research laboratory that provides state-of-the-art instrumentation, expertise, and infrastructure to carry out biomedical research utilizing the unique capabilities provided by high field MRI and MRS methodology. The central aim of the research conducted in CMRR is to non-invasively obtain functional, physiological, and biochemical information from intact biological systems and use this capability to probe biological processes in health and disease. The Center is housed in a freestanding ~34,000 square foot facility and is currently equipped with seven high field magnets with magnetic field strength of 3 Tesla and greater. Funded by NIH as a Biotechnology Research Resource for High Field Magnetic Resonance Imaging and Spectroscopy, and supported by numerous governmental and private foundations, CMRR core faculty have made significant and pioneering contributions in biological applications of magnetic resonance techniques and possess unique expertise in very high field uses of this methodology. Local resources within CMRR include Linux servers with up-to-date processing and memory capabilities, and adequate storage space. These local resources are used to accomplish testing of various image processing methodologies, simple pre- and post-processing, and other less compute-intensive processing streams. CMRR local resources are flexible, accommodating Windows, Mac, and UNIX virtual machines, and allow for Windows Terminal Server utilities. Dr. Quevedo and Dr. Ugurbil have been collecting data for the various ongoing pilot neurofeedback and emotion regulation studies as well as for K01 and NARSAD at CMRR using one of the 3 Tesla Prisma scanners with a 32 Channel receive only head coil (pictured below). The team has access to all CMRR's resources. The CMRR staff have trained all personnel on MRI safety, how to operate the MRI, and how to run the full protocol for neurofeedback pilot studies.

3T Prisma MRI Scanner

A 3T Prisma Scanner will be employed to deliver the neurofeedback intervention.

Mock MRI Scanner

To allow participants proper time to adjust to the environment of an MRI scanner before the actual scanning intervention, we will use a mock MRI scanner.

University of Minnesota Medical Center (UMMC) Child and Adolescent Psychiatry Clinics and Hospital Services. UMMC Psychiatry Clinics provide comprehensive psychiatric care for children and Participants with a broad range of psychiatric disorders. Specialty clinics include the Child and Adolescent Mood Disorders Clinic, and the Child and Adolescent Anxiety Disorders Clinic. Dr. Quevedo's and her study clinician team are integrated with and in proximity to all these services which facilitates the timely recruitment of the target sample of Participants and young adults exhibiting suicide ideation or behavior. Just two floors above the PI and research staff's offices in the Department of Psychiatry, is a 25-bed inpatient Adolescent Crisis Stabilization Unit. Many of the patients there were referred to Dr. Quevedo's K01 and NARSAD study with the help of the unit staff. The study successfully recruited approximately 130 depressed Participants in Minnesota.

The Institute of Child Development (ICD). Housed in the Department of Child Psychology at the University of Minnesota, ICD has been a premier center of scholarship, teaching, and outreach devoted to the understanding and fostering of child development since it was founded in 1925. Coursework and research activities focus primarily on the central cognitive, social, emotional, and psychological processes that underlie the development of infants, children, and participants. From its inception, a key tenet of the Institute has been to "give away" child psychology. This philosophy has created an environment rich with collaborations, new ideas, and exciting interdisciplinary work.

The Minnesota Supercomputing Institute (MSI). The University of Minnesota's Supercomputing Institute (MSI, www.msi.umn.edu) offers resources to carry out image processing that is extremely computing-intensive. Dr. Quevedo and her team have taken advantage of these resources, which consist of several supercomputing systems. University of Minnesota faculty members submit research proposals to the MSI committee every 6 months, and they award compute time based on individual project needs. Technical support for both resources is readily available. Additionally, Dr. Quevedo has already established the necessary programming needed to carry out the currently proposed data analysis method, both locally and on the supercomputer. All systems are compliant with the University of Minnesota, Academic Health Center, and Institutional Review Board recommendations on safe and secure computing.

University of Minnesota Department of Psychiatry Ambulatory Research Center (ARC). Located next to the main offices in the Department of Psychiatry, the ARC provides a comfortable convenient space for conducting research visits. ARC facilities include 5 interview rooms, a fully equipped exam room, and a computer testing room. Most clinical researchers in the psychiatry department take advantage of this resource, and thus it provides a setting to interact with other researchers and to share valuable resources.

The Emily Program. The Emily Program sees roughly 100 new patients per month and has a large cohort of about 2,500 patients at all ages in active treatment for anorexia nervosa, bulimia nervosa, binge eating, compulsive overeating, obesity, and other specified feeding and eating disorders. Suicidal ideation and attempts are highly prevalent in this population. This program has been a highly successful recruitment site for a wide variety of types of studies, including studies of suicidality. This study will recruit young patients who have clinically significant symptoms but who do not have a diagnosis of a specified eating disorder.

City of Minneapolis School Based Clinics. The Minneapolis Department of Health and Family Support (health department) School Based Clinics Program (SBC) provides comprehensive, accessible, teen-friendly health care to Participants. The SBC offers its students easy access to primary care and mental health services because the clinics are located where teens spend most of their day: in school. SBC Director of Mental Health Services, Marie Capra M.A. LMFT, and the other SBC therapists, will work with Dr. Quevedo and her research staff to recruit students 11-18 years old exhibiting suicidal ideation or past suicide attempt that attend the six high schools that have an SBC. Dr. Quevedo has had ongoing recruitment collaboration with Marie Capra and the SBCs over the past several years during her K01 adolescent depression study.

The Washburn Child Center. The Washburn Child Center is a leader in helping children with social, emotional, and behavioral problems and their families, serving children from birth to age 18. They have over 130 years of experience in assisting high risk children in the Minneapolis area. As a community mental health center focused on children's mental health, Washburn Child Center strives to integrate innovative research into program practice, implement meaningful evaluation methods and provide effective training and consultation for agency staff and community collaborators. The PI has an active collaboration with Washburn Child Center and their Clinical Director, Arlene Shatz, who has contributed to her success recruiting 65 depressed participants for her K01 study on adolescent depression. Washburn Child Center will be an excellent source of continued collaboration and source of recruitment for this study.

Prairie Care. Prairie Care is a large provider of mental health services in the state of Minnesota who receives thousands of Participants and young adults, many of them in partial or full hospitalization due to suicide attempts or suicide related acts. Paula Okorafor, MA, LP is a clinic supervisor and therapist there with whom the PI has collaborated with in the past for recruitment. The PI has maintained

an active collaboration with Prairie Care now for 4 years and they have been a steady source of referrals for research. Prairie Care is still growing in the state of Minnesota and the spread of their services will likely double within the next year or two.

The Center for Neurobehavioral Development (CNBD). Dr. Quevedo is a faculty member of the Center for Neurobehavioral Development. The CNBD is a unique and valuable interdisciplinary organization where researchers and clinicians from a diverse array of departments including neuroscience, pediatrics, neurology, psychiatry, psychology, and the Institute of Child Development (ICD) come together in an effort to identify the underpinnings of neurodevelopment. There are many experts that participate in research relevant to adolescent depression including stress neurobiology, cognitive neuroscience and neuroaffective development. Through this group Dr. Quevedo has already established a network of collaborators from a variety of fields that will facilitate the development of hypotheses and enriched translational research. Through its regular activities (12 colloquia per year, monthly Pediatric Imaging Group meetings, social functions with visiting scholars, etc.), the CNBD provides a convenient setting for discourse among investigators.

The Clinical and Translational Science Institute. The Clinical and Translational Science Institute (CTSI) at the University of Minnesota's Academic Health Center is one of approximately 60 medical research institutions working together to improve the way clinical and translational research is conducted nationwide, enhancing its efficiency and quality. CTSI aims to accelerate the process of translating laboratory discoveries into treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers. As a faculty member of the University of Minnesota, Dr. Quevedo is able to utilize the facilities and professional services offered through CTSI, including CTSI staff that support monitoring and guidance for ethical research practices.

University of Minnesota School of Public Health. The School of Public Health has 130 full-time faculty and instructors, as well as many other affiliated faculty members who advance the mission of the school and help forge tomorrow’s public health leaders. There are four divisions of faculty within the School of Public Health, biostatistics, environmental health sciences, epidemiology and community health, and health policy and management.

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