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Project Title: Neural mechanisms of meditation training in healthy and depressed adolescents: An MRI connectome study

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Clinical Intervention Study Protocol

Version 1.2

FULL PROTOCOL TITLE

Neural mechanisms of meditation training in healthy and depressed adolescents: An MRI connectome study

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Tool Revision History

Version Number: 1.2
Version Date: 06/22/2020
Summary of Revisions Made: (1) Delivery of the intervention over Zoom; (2) First visit Part A that includes consenting and questionnaires will be conducted over Zoom, using DocuSign; (3) All source documents will be signed and stored electronically in DocuSign; (4) Assessments including MRI scans to be completed within 4 weeks before/after the intervention; (5) Clarified that reported adverse events have to meet the provided definition of an adverse event; (6) Study Timeline updated; (7) Inclusion criterion added: “Access to a smartphone, a tablet or a computer, on which program “Zoom” can be run for remote participation in the intervention”.

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PARTICIPATING STUDY SITES

It is a single site study: please see the names and addresses above.

PRÉCIS

Study Title

Neural mechanisms of meditation training in healthy and depressed adolescents: An MRI connectome study

Objectives

The **primary objective** will be to study changes in putamen structural connectivity in healthy teens with meditation training. **Hypothesis**: Putamen structural node strength will increase in the training group compared to controls.

R61 Go/No-Go Criteria. Detect an effect size (a threshold of Cohen's d > 0.20) in changes of the primary mechanistic outcome (**Putamen structural node strength**) by the described meditation training in 100 healthy adolescents that are 14-18 years old and retain at least 80% of randomized participants for primary outcome measurement at the end of the study regardless of adherence to the intervention.

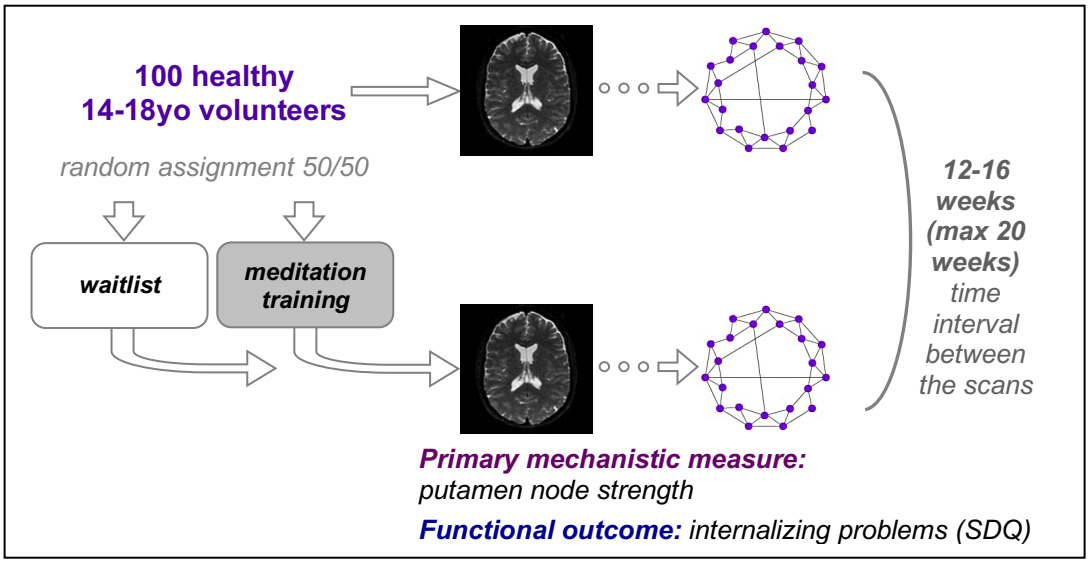
The **secondary objective** will be to study changes in emotional problems in healthy teens with meditation training. **Hypothesis**: There will be a significant decrease in emotional problems measured with the Strengths and Difficulties Questionnaire (SDQ) in the training group compared to controls.

Design and Outcomes

The current research study design will utilize an individually randomized group treatment, open-label, waitlist-controlled clinical trial to test the efficacy and safety of our innovative mindfulness meditation intervention (Training for Awareness Resilience and Action [TARA]) on the primary outcome (Putamen structural node strength) and secondary outcome (emotional problems measured with the Strengths and Difficulties Questionnaire [SDQ]) in healthy adolescents between the ages of 14 to 18 years old.

Please see below, Section 6.1 (Schedule of Evaluations), for detailed schedule and type of evaluations to be performed during the study.

R61 Overview Diagram of Study Design:



Interventions and Duration

The current study will specifically compare 12-week group meditation training intervention (TARA) with a waitlist control group. Each adolescent participant will be on study for the period of 12-weeks.

Sample Size and Population

The target population for the current study will be 100 healthy female and male adolescents that are between the ages of 14 to 18 years old who are randomly assigned to the 12-week meditation training intervention (TARA) or waitlist control group (50 healthy female and male adolescents between the ages of 14-18 years will be assigned to the 12-week meditation training intervention, and 50 healthy female and male adolescents between the ages of 14-18 years will be assigned to the waitlist control group). Randomization will not be stratified.

1. STUDY OBJECTIVES

1.1 Primary Objective

The **primary objective** will be to study changes in putamen structural connectivity in healthy teens with meditation training. **Hypothesis**: Putamen structural node strength will increase in the training group compared to controls.

R61 Go/No-Go Criteria. Detect an effect size (a threshold of Cohen's d > 0.20) in changes of the primary mechanistic outcome (**Putamen structural node strength**) by the described meditation training in 100 healthy adolescents that are 14-18 years old and retain at least 80% of randomized participants for primary outcome measurement at the end of the study regardless of adherence to the intervention.

1.2 Secondary Objectives

The **secondary objective** will be to study changes in emotional problems in healthy teens with meditation training. **Hypothesis**: There will be a significant decrease in emotional problems measured with the Strengths and Difficulties Questionnaire (SDQ) in the training group compared to controls.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

According to the World Health Organization (WHO), major depressive disorder (MDD) is the current leading cause of disability worldwide (Ferrari et al., 2013) and adolescence is an especially vulnerable period for the onset of depression. Depression has a prevalence by the end of adolescence of 20% (Brent & Birmaher, 2006) affecting the development of emotional, cognitive, and social skills which elevates the risk for suicide, substance use disorders, legal problems, physical illness, exposure to negative life events, early pregnancy, academic difficulties, family and friend problems, work problems, and poor psychosocial functioning (Birmaher et al., 2007; Essex et al., 2003; Infante et al., 2007). Depression during adolescence confers a 2- to 3-fold increased risk for adulthood depression (Pine et al., 1998). It is therefore of great importance both to develop prevention programs promoting emotional health and to intervene early with effective treatment of adolescent depression. Successful interventions during adolescence, when brain plasticity is peaking, may recover the aberrant neurocircuitry involved in emotional health.

2.2 Study Rationale

Non-pharmacologic approaches are particularly attractive due to the elevated risks of side effects related to the use of psychotropic drugs during development (Hetrick et al., 2007). Mindfulness meditation approaches are being explored for providing systematic training in emotional health (Vago & Silbersweig, 2012) and for treatment and prevention of depressive relapse (Kuyken et al., 2016). Our group has provided evidence that a meditative training (the same training we plan to use in our proposed study) can result in significantly strong effects of depressive symptom reduction in depressed adolescents (Henje Blom et al., 2016).

In the proposed study, we will use a type of **secular mindfulness meditation** practiced in the Training for Awareness, Resilience, and Action (TARA) (Henje Blom et al., 2014). The training was conceived in Dr. Yang's (co-PI) lab at UCSF as a treatment program for adolescent depression. It is a semi-manualized 12-week group intervention, informed by mindfulness- and yoga-based techniques, and it takes into account developmental aspects of the adolescent brain that is still in the process of maturation (Henje Blom et al., 2014). TARA training includes several embodied mindfulness meditation practices (breathing techniques, yoga-based movements, and guided meditation), which are accompanied by short psycho-educational presentations and group discussions. A more detailed outline of the TARA training is presented in the "5.1 Interventions, Administration, and Duration" section below. The TARA program has shown excellent retention rates, positive participants' feedback, and improved functional outcomes (Henje Blom et al., 2016).

Scientific Rationale Behind the Hypothesized Primary Mechanism

In the center of our hypothesis is the node strength of the putamen, a region previously associated, on one hand, with the onset of meditation practice (Baerentsen et al., 2010) and attenuated shrinkage with age in Zen meditators (Pagnoni & Cekic, 2007), and on the other hand, with love, compassion, anticipation of pleasure and responses to increasing intensity of happiness (Bartels & Zeki, 2004; Klimecki et al., 2013; Surguladze et al., 2003). The graph theory measure of node strength (w) represents the sum of the edge weights connecting node i to all other nodes and highlights the centrality of the node within the network: $w_i = \sum_{j=1}^{n} a_{ij}$, where a_{ij} is the edge weight between nodes i and j, and n is the number of nodes. Importantly, it is not an isolated characteristic of a brain region but encompasses multiple white matter fiber projections connecting it, in the case of putamen, to motor, somatosensory cortices, limbic systems, and, to the largest degree, to frontal areas including the **prefrontal cortex** (Verstynen et al., 2012).

Here, we propose a **model** of how meditation training positively affects emotional health in healthy and depressed youth, where increase of the putamen's node strength is the hypothesized primary mechanism (Fig. 1). Our model is based on Garland Positive Reappraisal model and includes the neural mechanism, which links meditation practice to emotional health. Mindfulness meditation promotes non-evaluative and non-judgmental awareness in response to stimuli and even though increasing positive affect is not a goal per se in this type of meditation, the Positive Reappraisal theory suggests that mindfulness allows for a decentered mode of awareness from which new positive cognitive appraisals of self and world can be made (Garland et al., 2009) (Fig. 1). Primary appraisal of a stressor stimulus is usually followed by a cognitive process of secondary appraisal in which one's resources and coping options are weighted against the perceived demands of the situation.

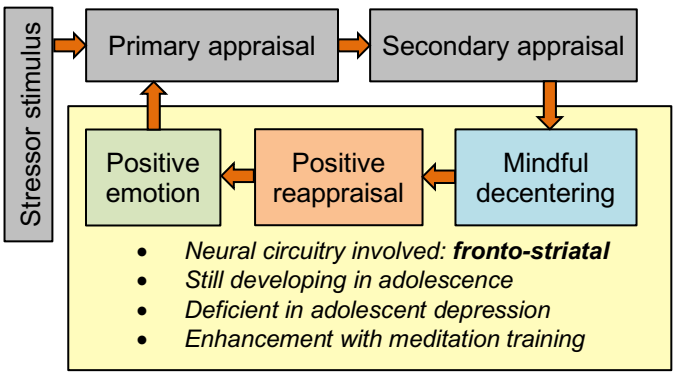


Figure 1. Proposed model of how meditation exerts its positive effects on emotional health in healthy and depressed adolescents. Based on Garland model of mindfulness and Davey model of adolescent depression.

Mindful decentering from this stress appraisal, wherein one attends to the dynamic process of consciousness itself rather than its contents, allows one to reappraise the event in a positive manner by attributing to it new meaning, in a way that engenders hope, resilience and creativity. The reappraisal then results in positive emotions such as compassion, trust, confidence, which in turn influence subsequent appraisal processes.

The role of putamen connectivity in meditation. We hypothesize that the transition from mindful decentering to positive emotion involves the fronto-striatal circuitry, specifically, the node strength of the putamen. The putamen has been implicated in both, onset of meditation practice (Baerentsen et al., 2010) and during continuous meditation by Lazar et al. (2000) and Tang et al. (2009), who reported increased activity in the putamen. Baerentsen et al. observed patterns of activations and deactivations in the brain, including pronounced activation in putamen with the onset of meditation practice. Remarkably, a 65% increase of endogenous dopamine release was observed in the striatum during meditation (Kjaer et al., 2002). We expect that regular engagement of the putamen will increase myelination of the white matter tracks connecting it to other regions (including the **prefrontal cortex**, PFC), which can be probed by using diffusion MRI fractional anisotropy (FA) indices as network weights. Our **preliminary results** in healthy adolescents using diffusion tensor imaging (DTI) and tractography (Fig. 2) show a medium-large effect of the putamen node strength increase during the meditation training compared to the waiting period and correlation of this increase with the self-reported amount of meditation practice. All specific statistics will be discussed in following sections.

The role of putamen connectivity in emotional health. The putamen's involvement in reward-related behavior and emotions has been well-studied (Lanciego et al., 2012). The basis of hedonic feelings has been studied through many different paradigms demonstrating association with striatal regions including the putamen (Gorwood, 2008). Increased functionality of the putamen is expected to decrease internalizing emotional problems such as feeling unhappy/worried/fearful and induce well-being and a more positive emotional tone. In alignment with this function of the putamen and its stimulation through meditation, our **preliminary results** in healthy adolescents show a decrease in emotional problems (internalizing subscale of the Strengths and Difficulties Questionnaire, SDQ) during the meditation training compared to the waiting period. We also observed in our **preliminary data** an association between the decrease in emotional problems and the increase of the putamen node strength, which provides support for the proposed model (Fig. 1).

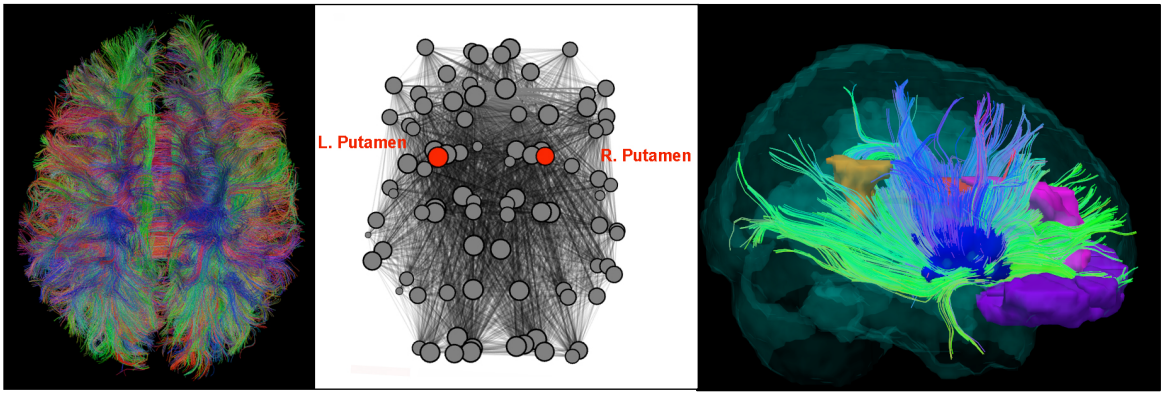


Figure 2. From left to right: DTI-based whole-brain tractogram in a healthy adolescent (left image); the corresponding graph depicting the connectome with putamen nodes highlighted in red (middle image); tracks connecting the putamen with cortical regions in an adolescent brain (right image).

The role of putamen connectivity in adolescent depression. We also expect that meditation training will benefit adolescents suffering from depression by employing the described mechanism. Anhedonia – the decrease or loss of the ability to experience pleasure and happiness – is a key characteristic of major depressive disorder. Our **preliminary results** show that structural connectivity of the putamen is lower in depressed adolescents compared to healthy controls and that this hypoconnectivity is correlated with anhedonia, as we will show in more detail below. Gabbay et al. also reported abnormal resting-state functional connectivity of the putamen in depressed adolescents that significantly correlated with their levels of anhedonia (Gabbay et al., 2013). Since adolescence is a critical neurodevelopmental time period with significant remodeling and maturation of the dopaminergic reward system in the brain, Davey et al. have proposed a **neurodevelopmental model** that hypothesizes teen depression is due to the failure of the proper neurodevelopment of greater connectivity between the **reward areas** (i.e., **putamen**) and **prefrontal cortical** (PFC) areas (Davey et al., 2008). Their theory proposes that experiencing pleasurable and positive emotions is necessary for the proper neurodevelopment of the reward system during adolescence and that the lack of these experiences leads to the onset of adolescent depression. Mindfulness approaches are being explored for treatment and prevention of depressive relapse in adults (Kuyken et al., 2016). We have previously demonstrated that a meditative training (the training that will be used in this study) can result in a significantly strong effect of depressive symptom reduction in clinically depressed adolescents (Henje Blom et al., 2016). For these reasons, we chose to study meditation training for depressed adolescents as the optimization strategy for the R33 phase. As in the R61 phase, we expect increases in putamen node strength with practice of meditation. We expect that the mechanistic effect in the putamen will be amplified in the population of depressed as compared to healthy teens, which may reflect normalization of the putamen function. In our **preliminary study** of healthy adolescents, we observed a stronger increase of putamen node strength in those teens with lower baseline node strength. Our results in a small sample of adolescents with MDD show feasibility of recruitment and MRI scanning, and they also indicate a stronger increase of putamen node strength compared to healthy teens.

The proposed project will advance knowledge of the mechanism of action of meditation training by applying the most advanced neuroimaging approaches and by testing the proposed novel model (Fig. 1).

Biological and Psychological Relevance

The study population in the R61 phase will be healthy adolescents between the ages of 14-18 years. By this age, brain systems implicated in basic cognitive processes reach adult levels of maturity, whereas those that are active in the reward system are undergoing significant remodeling and neurodevelopmental maturation (Davey et al., 2008). The most rapid synaptic pruning is thought to occur between the ages of 12 and 16.5 years (Campbell et al., 2012), thus presenting an opportunity for long-lasting beneficial adaptations. In the R33 phase, we plan to study youth between the ages of 14-18 years who suffer from mild to moderate depression and who are under the care of a primary care doctor. During this critical time (14-18 years), the incidence of depression peaks and shows a dramatic, approximately three-fold increase (Hammen & Rudolph, 1996).

3. STUDY DESIGN

The present research study design will utilize an individually randomized group treatment, open-label, waitlist-controlled clinical trial to test the efficacy and safety of our innovative mindfulness meditation intervention (Training for Awareness Resilience and Action [TARA]) on the primary outcome (Putamen structural node strength) and secondary outcome (emotional problems measured with the Strengths and Difficulties Questionnaire [SDQ]) in healthy adolescents between the ages of 14 to 18 years old.

The specific unit of assignment and unit of observation are the individual study participants.

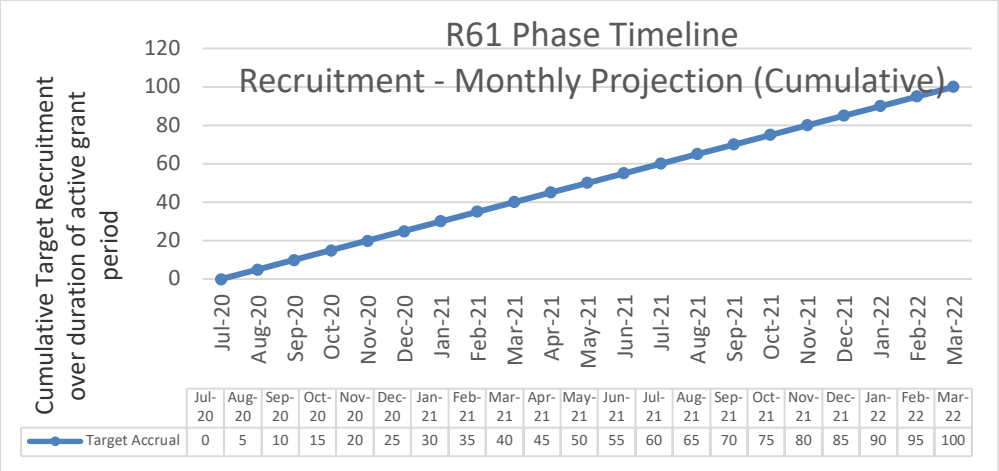
Primary outcome: Putamen structural node strength

Secondary outcome: Emotional problems measured with the Strengths and Difficulties Questionnaire (SDQ)

The study population are 100 healthy adolescents that are 14-18 years old, who are randomly assigned to the intervention or waitlist control group (50 assigned to intervention, 50 assigned to waitlist control who will later receive the intervention).

The entire study will take place at the University of California, San Francisco (UCSF). More specifically, all of the MRI scans will take place at the UCSF Mission Bay campus. All of the TARA group interventions and subject interviews will take place remotely over Zoom.

The approximate duration of subject enrollment period for the entire trial will be 21 months (please see below, R61 Phase Timeline). We plan to run 5 intervention groups and 5 waitlist control groups. The intervention duration is 1.5 hours per week for 12 weeks, and MRI scanning and clinical assessments will be performed within 2 weeks (maximum 4 weeks) before and after the 12-week intervention. Thus, each individual participant who is randomly assigned to the intervention will be followed for a total duration of up to 20 weeks (12 weeks of intervention plus up to 4 weeks before the start of the intervention plus up to 4 weeks after the end of the intervention). The individual participants who are randomly assigned to the waitlist control will be similarly followed for approximately 20 weeks.



Intervention: 12-week group meditation training, Training for Awareness, Resilience, and Action (TARA).

We will use computer-generated randomization with variable blocks sizes of 4, 6 and 8. Individuals will be randomized with no stratification, matching or constraints except the permuted blocks. We will permute 8 blocks of size 8, 2 blocks of size 6, and 4 blocks of size 4. The treatment assignments will be 1:1 within each block and assignments within a block will be permuted. The only masking will be in the administration of questionnaires and in the interpretation of putamen node strength.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Healthy female and male adolescents, 14-18 years old.

We will use Medical History form a (NCCIH Version 1.0). The required current status of participants within 4 weeks prior to randomization is absence of current medical, neurological, or psychiatric conditions.

Fluency in English.

Access to a smartphone, a tablet or a computer, on which program “Zoom” can be run for remote participation in the intervention.

4.2 Exclusion Criteria

- Subjects younger or older than 14-18 years old.
- Subjects who are not healthy. We will use Phone Pre-Screener and Medical History form a (NCCIH Version 1.0) to exclude any adolescent who has been clinically diagnosed with any significant medical disorder that would prevent him or her from performing yoga-based movements (e.g., cerebral palsy), neurological disorder (e.g., multiple sclerosis, severe

head trauma) or mental health disorder (e.g., psychosis, schizophrenia, schizoaffective disorder, major depressive disorder, bipolar disorder, ADHD, autism spectrum disorder, anorexia nervosa, PTSD) or has intellectual disability, or suicidal ideation or attempt in past 3 months.

- Subjects who are taking any psychotropic medication.
- MRI contraindications (ferromagnetic objects on or inside the body, e.g., braces) and pregnancy.
- Pregnancy or any plans to become pregnant during the study is an exclusion criterion for entrance into the study. Women of reproductive capability will be asked to employ at least one of the following allowable contraception methods until they complete their second MRI scan: birth control implant, birth control shot, birth control patch, birth control pill, condom, internal condom, birth control sponge, cervical cap, spermicide, fertility awareness (calendar method), outercourse and abstinence.
- The study's pregnancy-related policy and procedure are as follows. First, all female participants will be asked to fill out a pregnancy screening questionnaire and then take a urine pregnancy test immediately prior to entering the MRI scanner room. Any subject that is either pregnant or might possibly be pregnant are not allowed to enter the MRI scanner room. Results of the urine pregnancy screening test will be shared with the adolescent subject only and not with the adolescent's parents or legal guardians. As per California state confidentiality laws, the results of pregnancy tests in minors cannot be shared with the minor's parent or legal guardian without the written permission of the minor. If the pregnancy test is positive, we will counsel the teen and give her referrals to teen pregnancy resources such as Planned Parenthood. If the participant is pregnant, the participant is not allowed to enter the study until the pregnancy is over. Second, if the participant who is in the intervention group becomes pregnant during the course of the study after the first MRI scan, she will be allowed to finish participating in the group intervention since there are no known potential adverse effects on the fetus due to meditation. However, although there are no known adverse negative effects of MRI scans on the fetus, we have decided to be conservative in our study and not allow participants who become pregnant during the study after the first MRI scan to have the second MRI scan in order to minimize any potential risk to the unborn fetus.
- Not allowable: Current mindfulness training (e.g. MBSR, MBCT, DBT) and/or practice with a typically sitting meditation or yoga of 20 or more minutes two or more times per week within 60 days prior to study entry.
- Potential adolescent subjects with current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to the study requirements will be excluded and not allowed to enter the study. We will use the Brief Screener for Tobacco, Alcohol, and other Drugs (BSTAD) developed by National Institute on Drug Abuse

(NIDA) to determine higher risk subjects who will be excluded: https://www.drugabuse.gov/adolescent-substance-use-screening-tools.

- Potential subjects with an inability or unwillingness to give written informed assent or whose legal guardian/representative are unable or unwilling to give written informed consent will be excluded and not allowed to enter the study.

4.3 Study Enrollment Procedures

Recruitment of potentially eligible participants will be primarily performed using IRB-approved ads on internet sites such as Instagram, Facebook, Craigslist, Nextdoor. Moreover, recruitment will be performed in the San Francisco Unified School District (SFUSD) using IRB-approved flyers. The SFUSD is the seventh largest school district in California, educating over 57,000 students every year. We have substantial experience of working successfully with SFUSD Wellness Centers and creating flyers that attract the attention of candidate participants. Our flyers have been previously deemed to have a clear educational enrichment purpose for SFUSD and we have always successfully obtained permission to distribute the printed flyers as well as online announcements to SFUSD staff, family, and students through

http://www.sfusd.edu/en/news/request-to-distribute.html.

Due to COVID-19, we have transitioned to implementing the vast majority of our subject recruitment efforts using the internet and online methods. When the school districts (i.e., SFUSD) begin to allow students to enter the school campuses, we will resume posting our UCSF IRB-approved flyers at the several different school campuses again. Any interested adolescent and/or parent of an adolescent who phones or e-mails either the PIs or research assistants in response to the UCSF IRB-approved flyer will be considered for the study.

Ancillary recruitment strategies: In addition to recruiting from SFUSD, we plan to also recruit healthy adolescents for our study through posting our UCSF IRB-approved recruitment flyers at several other recruitment sites located throughout San Francisco and the San Francisco Bay Area.

Prior to enrollment into the study, all potential subjects will be initially screened using a Phone Pre-Screener. Study staff performing the screening by telephone will complete the checklist to ensure that the potential participant meets eligibility criteria to enter the study (please see included Phone Pre-Screening form).

Adolescents and their parents/guardians will be screened using a semi-scripted telephone screening procedure designed to elicit inclusion/exclusion information and provide additional information about the study to the caller. The parent and adolescent will provide **verbal consent** to answer some questions over the telephone to pre-screen the adolescent regarding eligibility (e.g. age 14-18 years, healthy, English-speaking) as well as **verbal consent** to study participation, and availability

for study assessments and classes. The study procedures, including what is involved in participating in the training, as well as the MRI visits will be described to potential participants and their parents. The goal is to ensure they understand the commitment involved in study participation. Those who do not meet eligibility criteria will be told that they are not eligible to participate. **First visit**: Those who meet inclusion criteria and give **verbal consent** will schedule the first visit which will include the questionnaire-based assessments (First visit Part A) and baseline MRI scan (First visit Part B). The **consent form** will be mailed or emailed for review prior to the visit. At the First visit Part A, which can be conducted over Zoom, the researcher will first review the **consent form** with the adolescent and the parent/guardian, and they will **both sign the form** using DocuSign. Electronic copies of all consent forms will be provided to the participant and to the parent or legal guardian, as well as the Experimental Subjects Bill of Rights. No adolescents will be contacted or screened by the study team before parental verbal consent is obtained. The exception is the 18-year-old participants who do not need parental consent.

We will use computer-generated randomization with random blocks sizes ranging from 4 to 8 in order to assign a participant to either the TARA intervention group or the waitlist control group.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The TARA intervention is delivered in a semi-manualized form in 12 consecutive, weekly 1.5-hour sessions by two facilitators (who are trained by Dr. Henje Blom). In case of a remote delivery of the intervention, a group size of 8-10 participants allows for a good overview of everyone in the group. Participants will be instructed by the TARA facilitators how to best create a quiet, temperature-controlled, comfortable practice space in their home, and how to best use Zoom and camera on their device. Each participant will receive from us props for their practice (a yoga mat, a meditation pillow, an eye pillow, etc.). Daily home practice of TARA skills will be encouraged and audio recordings with guided meditations will be provided. The **outline** of the **TARA intervention** is as follows (for details, see *Blom Henje et al., 2014*): *Module 1*: focuses on the ability to create a calm and safe inner state through breathing, yoga-based movement and guided "body-scan" meditations. A brief psycho-educational module on the psychophysiology of stress and respiration is provided. *Module 2*: includes attention training first targeting external stimuli, followed by sensory stimuli and interoceptive awareness. Psycho-education is provided on an adapted neuroscience model and the importance of sleep and healthy eating for emotional health. *Module 3:* focuses on recognizing, labeling, and communicating emotions. By aiding participants in identifying their emotions and applying skills from modules 1 and 2, the core skills are applied in social interaction. In *Module 4* a more cognitively based behavioral activation approach is introduced, including understanding of social triggers of negative emotions and one's own experiential avoidance strategies and how they may impede obtaining desired life goals. A parallel focus on defining personal core values and linking them to behavior activation is a thread throughout the intervention that serves as a motivational force to increase sustainability and future engagement in salutogenic activity. The meditative practices are continued in all modules.

The attached **TARA Manual** provides extensive details on the content of each TARA session (please see Appendix).

The TARA sessions will take place remotely over Zoom.

TARA training facilitators: Two facilitators are provided for each class who can support each other in creating a safe environment for the participants. The facilitators have many years of their own mindfulness practice, so that they may effectively model the mindfulness practices and know from their own experience the effect of the different practices that are introduced to the participants during the TARA training. We have an available pool of eight TARA facilitators who are officially trained to teach TARA. The following four facilitators from this available pool of eight are the primary facilitators for this project:

Catherine Shaddix, Psy.D, is a graduate of the doctoral program in clinical psychology at the Wright Institute in Berkeley, CA. She completed her pre-doctoral internship at the Infant, Child, and Adolescent Division of Psychiatry at the UCSF San Francisco General Hospital. Her dissertation research, conducted at the UCSF Osher Center for Integrative Medicine, was a long-term follow-up study of mindfulness training. In 2015, she was also an intervention design team member and facilitator for the TARA groups in adolescents.

Jennifer Shao, MFT, received her Masters in Clinical Psychology at San Francisco State University. She is a school-based clinician at Ann Martin Center, CA. She has provided individual therapy sessions to children, family therapy and parenting skills training, collateral consultation and psychoeducation to parents, teachers, school staff and other providers. Jennifer has facilitated mindfulness and play therapy groups within the school setting. Since 2016, she has been co-teaching TARA training for adolescents.

Jonathan Weinstock, B.A., has been Program Manager and Mindfulness Teacher at Edgewood Center for Children and Families for over 16 years. Edgewood Center for Children and Families has served the San Francisco Bay Area for over 150 years by providing the full continuum of behavioral and mental health services to children, youth, and families. Jonathan Weinstock has been facilitator for TARA groups in adolescents since 2015.

Lisa Lin Baldini, B.A., is expecting her Doctoral Degree in Clinical Psychology from PGSP-Stanford PsyD Consortium, Palo Alto, California in 2019. She has experience teaching TARA groups and she has published scientific peer-reviewed articles on TARA training. In her doctoral dissertation, which she defended in 2018, Lisa Baldini studied the effects of TARA on self-compassion.

Potential adverse effects from the TARA intervention: Participants could experience restlessness or some difficult emotions, like sadness or anger, during some of the class activities or home assignments. To minimize the risks to subjects and this potential adverse effect from the TARA intervention, If participants experience difficult emotions during the TARA intervention, they can stop the activity and speak to the class leader or study staff. The class leader will talk about how to handle difficult emotions that come up during home assignments at the first class, and

throughout the course as needed.

5.2 Handling of Study Interventions

To ensure the completeness and accuracy of the data, the study intervention accountability records (i.e., On Study Visit Checklist) will be completed at each of the TARA intervention sessions when the participants receive the TARA intervention training. (Please see On Study Visit Checklist form in Appendix)

The attached **TARA Manual** provides extensive details on the content of each TARA session (please see Appendix).

The study subjects/patients will know which study group they have been assigned to (i.e., TARA intervention or waitlist control). Thus, by necessity, they will be *only* unblinded to the study group assignment.

The TARA Instructors/Practitioners must—by necessity—be *only* unblinded to the study intervention group assignment in order to deliver the TARA intervention to the participants.

All of the Outcome Assessors will be blinded to study group assignment until after the database is locked. **In order to blind the Outcome Assessors to study group assignment, each adolescent subject will be assigned a unique numerical identifier to mask the identity of the subject and also mask any private information that is linked to the subject**. Coding and assignment of the unique numerical identifier will occur at the time of subject consent. This unique numerical identifier will be attached to all data acquired from adolescent subjects.

In order to maintain masking (i.e., blinding) of study group assignment, all of the participants will be clearly instructed *not* to discuss with any of the research study staff which study group they have been assigned to during the entire duration of the study.

The Data Analysts and Statistician will be blinded to the intervention group assignment until after the database is locked. **In order to blind the Data Analysts and Statistician to study group assignment, each adolescent subject will be assigned a unique numerical identifier to mask the identity of the subject and also mask any private information that is linked to the subject**.

The Data Analysts and Statistician will be unblinded after the database is locked at the time of the data analysis.

The Principal Investigators (PIs) will be blinded to the intervention group assignment during the entire course of the study until after the database is locked. **In order to blind the PIs to study group assignment, each adolescent subject will be assigned a unique numerical identifier to mask the identity of the subject and also mask any private information that is linked to the subject**.

Since the safety of all of the participants is of paramount importance, there is a risk of inadvertently unblinding of the co-PI, Dr. Yang, if a safety concern arises (e.g., suicidal ideation

in a participant). However, even if Dr. Yang is inadvertently unblinded in order to ensure the safety of the subject, Dr. Yang and Dr. Tymofiyeva will both remain blinded to both the Primary Mechanistic Outcome Measure and Clinical/Functional Outcome Measure for the entire duration of the study until after the database is locked.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All interventions are allowed while on study except for the following: mindfulness training (e.g. mindfulness-based stress reduction [MBSR], mindfulness-based cognitive therapy [MBCT], dialectical behavior therapy [DBT]) and/or practice with a typically sitting meditation or yoga of 20 or more minutes two or more times per week.

5.3.2 Required Interventions

There are no required interventions that are also required in addition to the TARA intervention which is the focus of this study.

5.3.3 Prohibited Interventions

The following interventions are prohibited while the participant is on study: mindfulness training (e.g. mindfulness-based stress reduction [MBSR], mindfulness-based cognitive therapy [MBCT], dialectical behavior therapy [DBT]) and/or practice with a typically sitting meditation or yoga of 20 or more minutes two or more times per week.

5.4 Adherence Assessment

Definition of Adherence: The proportion of volunteers randomized to TARA training who participate in at least 75% of the sessions. Adherence to the TARA study intervention will be assessed by recording the attendance of each of the participants at each of the TARA intervention sessions. We expect that at least 80% of participants on the TARA arm will attain this level of adherence. Please see below section on Data Analyses (Section 9.6) for description of how this information will be incorporated into the analysis of the study results.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Phone Pre-Screening	Screening, Baseline, Enrollment, Randomization: Visit 1 (Day 0)	Visit 2 (TARA 1)	Visit 3 (TARA 2)	Visit 4 (TARA 3)	Visit 5 (TARA 4)	Visit 6 (TARA 5)	Visit 7 (TARA 6)	Visit 8 (TARA 7)	Visit 9 (TARA 8)	Visit 10 (TARA 9)	Visit 11 (TARA 10)	Visit 12 (TARA 11)	Visit 13 (TARA 12)	Followup: Final Visit 14
Phone Pre-Screening	X														
Informed Consent Form		X													
Medical History		X													
Inclusion/Exclusion Criteria		X													
Enrollment/Randomization		X													
Demographics		X													
SDQ		X													X
MRI Screening Form & urine pregnancy test		X													X
MRI		X													X
Baseline Checklist		X													
CORS			X	X	X	X	X	X	X	X	X	X	X	X	X
CSRS			X	X	X	X	X	X	X	X	X	X	X	X	
On Study Visit Checklist			X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

These evaluations occur to determine if the candidate is eligible for the study.

Definitions of the column headings in the Schedule of Evaluations (Section 6.1): (1) Assessment refers to the specific assessments as listed in the first column that will be performed at each of the study visits; (2) Visit 1 (Day 0) refers to all of the assessments that will occur at the first study visit; (3) Visits 2 to 13 refer to the assessments that will occur at each of the study visits 2 through 13 which correspond to the TARA study intervention sessions 1 through 12 (i.e., Study Visit 2 is TARA study intervention session 1 since the first TARA study intervention session will take place on Study Visit 2); (4) Final Visit 14 refers to all of the assessments that will occur on the final study visit which will be Visit 14. Please note that in the above Schedule of Evaluations (Section 6.1), the AE and SAE forms only will be completed if an AE and/or SAE are reported by a participant. In addition, if a participant prematurely leaves the study, all of the assessments listed under the final study visit 14 column will be performed.

A phone pre-screening evaluation will occur to determine if the candidate adolescent is eligible for the study prior to the initial visit, and a screening evaluation will occur at Visit 1 (Day 0) to determine if the candidate is eligible to enter the study.

Consenting Procedure

A trained research staff member who will have at least a college degree (i.e., Bachelor's degree or higher) will perform the following informed consent process.

Adolescents and their parents/guardians will be screened using a semi-scripted telephone screening procedure designed to elicit inclusion/exclusion information and provide additional information about the study to the caller. The parent and adolescent will provide **verbal consent** to answer some questions over the telephone to pre-screen the adolescent regarding eligibility (e.g. age 14-17 years, healthy, English-speaking) as well as **verbal consent** to study participation, and availability for study assessments and classes. The study procedures, including what is involved in participating in the training, as well as the MRI visits will be described to potential participants and their parents. The goal is to ensure they understand the commitment involved in study participation. Those who do not meet eligibility criteria will be told that they are not eligible to participate. **First visit**: Those who meet inclusion criteria and give **verbal consent** will schedule the first visit which will include the questionnaire-based assessments (First visit Part A) and baseline MRI scan (First visit Part B). The **consent form** will be mailed or emailed for review prior to the visit. At the First visit Part A, which can be conducted over Zoom, the researcher will first review the **consent form** with the adolescent and the parent/guardian, and they will **both sign the form** using DocuSign. Electronic copies of all consent forms will be provided to the participant and to the parent or legal guardian, as well as the Experimental Subjects Bill of Rights. These forms will be kept in a locked filing cabinet and will not have participant ID numbers on them. No adolescents will be

contacted or screened by the study team before parental verbal consent is obtained. The exception is the 18-year-old participants who do not need parental consent. In case any changes may be required to the consent form, the PIs (Drs. Tymofiyeva and Yang) will review the consent document and make any changes as they decide are required to the consent form.

Screening

The allowable range of time prior to study entry during which all screening evaluations to determine eligibility must be completed will be 2 months.

The following screening evaluations will occur in the following sequence of events:

- Phone pre-screen. The phone pre-screen will occur first. If the potential participant meets eligibility criteria, they are invited to the first visit at UCSF (Visit 1). If the potential participant does not meet eligibility criteria during the phone pre-screen, they are thanked for their interest and informed that they do not meet eligibility requirements for the study. The phone prescreen must be done within 2 months of enrollment.
- Visit 1 (Day 0). If the potential subject meets eligibility criteria based on the initial phone pre-screen, they are invited to come to their first visit (Visit 1). During Visit 1 Part A, which can be conducted over Zoom, the following additional screening forms will be completed: (1) Medical History form that will ascertain if the patient has any current medical, neurological, or psychiatric illnesses that would exclude the subject from enrolling in the study; and (2) Inclusion/Exclusion Criteria form that will determine through a sequence of "yes" and "no" questions whether the subject meets the full inclusion and exclusion criteria to be allowed to enroll into the study. The Medical History form and Inclusion/Exclusion criteria forms must both be completed the same day as the enrollment into the study.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

The current study will utilize a single informed signed consent form that describes both screening and study procedures. Thus, in the current study, the enrollment date is defined as the date all of the screening criteria are met and the individual agrees to participate which is also the same date as the randomization date (i.e., Visit 1 [Day 0]). Please see above, Section 6.1, Schedule of Evaluations Table. The enrollment date will be recorded on a case report form (please see included Randomization and Enrollment form) along with the allowable window between screening and randomization (please see above section, "Screening", for the precise allowable time window between screening and randomization).

Baseline Assessments

The following baseline evaluations will occur on Visit 1 (Day 0) of the study:

- MRI brain scan. An MRI brain scan will be acquired at baseline to compare

against the final MRI brain scan that will be obtained at the final visit (Visit 14).

- Strengths and Difficulties Questionnaire (SDQ). Emotional problems will be assessed in all participants at baseline using the SDQ in order to compare with the SDQ that will be collected at the final visit (Visit 14).

Randomization

Computer-generated randomization will precede intervention administration in the current randomization study. The time window for randomization relative to completion of screening and baseline will be 24 hours (i.e., randomization as well as completion of screening and baseline will all occur the same day). The time window for initiation of study intervention relative to randomization will be 4 (four) weeks.

6.2.3 Blinding

There will be one unblinded research assistant (RA) who will be responsible for: (1) scheduling and helping set-up the delivery of the TARA intervention, and (2) providing unblinded case-by-case reports to the study Independent Monitors (IM); this RA will have no access to data and no involvement in data monitoring and analyses.

Since the Study subjects and TARA Instructors/Practitioners can not be blinded to the Intervention group assignment (please see below, Table 1 Blinding Table), there will not be an individual authorized to break the blind, circumstances for breaking the blind, or procedures for breaking the blind. Which stake holders will be blinded, what the stake holders will be blinded to, and the procedures for retaining the blind for the different stake holders for the intervention group assignment, primary mechanistic outcome measure, and clinical/functional outcome measure are described below in Table 1 (please see below, Table 1. Blinding Table).

Table 1. BLINDING TABLE

Stake holder	Intervention group assignment	Primary Mechanistic Outcome Measure	Clinical/ Functional Outcome Measure
Study subjects/Patients	*Not blinded* The study subjects/patients will know which intervention group they have been assigned to. Thus, by necessity, they will be *only* unblinded to the intervention group assignment.	*Blinded* The study subjects/patients will be blinded to the Primary Mechanistic Outcome Measure for the entire duration of the project.	*Blinded* The study subjects/patients will be blinded to the Clinical/Functional Outcome Measure for the entire duration of the project.
Instructors/ Practitioners	*Not blinded* The TARA Instructors/Practitioners must—by necessity—be *only* unblinded to the intervention group assignment in order to deliver the	*Blinded* All of the TARA Instructors/ Practitioners will be blinded to the Primary Mechanistic Outcome	*Blinded* All of the TARA Instructors/Practitioners will be blinded to the Clinical/Functional Outcome

	TARA intervention to the participants.	Measure for the entire duration of the study.	Measure for the entire duration of the study.
Outcome Assessors	*Blinded* All of the Outcome Assessors will be blinded to group assignment until after the database is locked. In order to blind the Outcome Assessors, each adolescent subject will be assigned a unique numerical identifier to mask the identity of the subject and also mask any private information that is linked to the subject. Coding and assignment of the unique numerical identifier will occur at the time of subject consent. This unique numerical identifier will be attached to all data acquired from adolescent subjects. Participants will be instructed not to discuss with any of the research study staff which group they have been assigned to during the entire duration of the study.	*Blinded* Neuroimaging Outcome Assessors will be blinded to clinical outcome assessments. Similarly, Clinical Outcome Assessors will be blinded to the neuroimaging outcome assessments. The clinical Outcome Assessors and neuroimaging Outcome Assessors will be separate study staff who will work in separate offices located on separate campuses at UCSF. The clinical Outcome Assessors and neuroimaging Outcome Assessors will not communicate with one another regarding the outcome of their separate assessments at any time point during the course of the study until after the database is locked.	*Blinded* Clinical Outcome Assessors will be blinded to the neuroimaging outcome assessments. Similarly, neuroimaging Outcome Assessors will be blinded to clinical outcome assessments. The clinical Outcome Assessors and neuroimaging Outcome Assessors will be separate study staff who will work in separate offices located on separate campuses at UCSF. The clinical Outcome Assessors and neuroimaging Outcome Assessors will not communicate with one another regarding the outcome of their separate assessments at any time point during the course of the study until after the database is locked.
Data Analysts/ Statistician	*Blinded* The Data Analysts and Statistician will be blinded to the intervention group assignment until after the database is locked. The Data Analysts and Statistician will be unblinded after the database is locked at the time of the data analysis.	*Blinded* The Data Analysts and Statistician will be blinded to the Primary Mechanistic Outcome Measure until after the database is locked. The Data Analysts and Statistician will be unblinded after the database is locked at the time of the data analysis.	*Blinded* The Data Analysts and Statistician will be blinded to Clinical/Functional Outcome Measure until after the database is locked. The Data Analysts and Statistician will be unblinded after the database is locked at the time of the data analysis.
Principal Investigators	*Blinded* The Principal Investigators (PIs) will be blinded to the intervention group assignment during the entire course of the study until after the database is locked. Since the safety of all of the participants is of paramount importance, there is a risk of	*Blinded* The PIs will be blinded to the Primary Mechanistic Outcome Measure during the entire course of the study until after the database is locked.	*Blinded* The PIs will be blinded to the Clinical/ Functional Outcome Measure during the entire course of the study until after the database is locked.

	inadvertently unblinding of the co-PI, Dr. Yang, if a safety concern arises (e.g., suicidal ideation in a participant). However, even if Dr. Yang is inadvertently unblinded in order to ensure the safety of the subject, Dr. Yang and Dr. Tymofiyeva will both remain blinded to both the Primary Mechanistic Outcome Measure and Clinical/Functional Outcome Measure for the entire duration of the study until after the database is locked.		

6.2.4 Followup Visits

The following study visits must be performed on the weeks indicated above in the Schedule of Evaluations (please see Section 6.1) plus/minus 5 (five) *working* days (i.e., Monday through Friday, not including weekends and holidays):

- Visit 1:
  - Informed Consent Form
  - Medical History Form
  - Inclusion/Exclusion criteria form
  - Enrollment/Randomization form
  - MRI Screening Form & urine pregnancy test
  - MRI brain scan
  - Demographics assessment (electronically in Qualtrics)
  - SDQ assessment (electronically in Qualtrics)
  - Baseline Checklist
- Visit 2 through Visit 13:
  - Child Session Rating Scale (CSRS)
  - Child Outcome Rating Scale (CORS) including the question: "Has there been any significant unfavorable change in your mental or physical health since last class?" (please see Appendix. Not a source document.)
  - Adverse Events (if answered Yes the question above in CORS)
  - Serious Adverse Events (if answered Yes to the SAE question in the Adverse Event form)
  - On Study Visit Checklist Form (modified to include Treatment Administration information)

6.2.5 Completion/Final Evaluation.

The following assessments will be performed at the participant's final visit (Visit 14):

- SDQ assessment (electronically in Qualtrics)
- MRI Screening Form & urine pregnancy test
- MRI brain scan
- Child Outcome Rating Scale (CORS) including the question: "Has there been any significant unfavorable change in your mental or physical health since last class?" (please see Appendix. Not a source document.)
- Adverse Events (if answered Yes the question above in CORS)
- Serious Adverse Events (if answered Yes to the SAE question in the Adverse Event form)
- Study Completion form.

For study participants who discontinue the study intervention early, all of the following assessments will be performed:

- SDQ assessment (electronically in Qualtrics)
- MRI Screening Form & urine pregnancy test
- MRI brain scan
- Child Outcome Rating Scale (CORS) including the following question: "Has there been any significant unfavorable change in your mental or physical health since last class?" (please see Appendix. Not a source document.)
- Adverse Events (if answered Yes the questions above in CORS)
- Serious Adverse Events (if answered Yes to the SAE question in the Adverse Event form)
- Study Completion form.

Potential reasons for early terminations: (1) participant moves away to a distant part of the country or another country outside of the United States, (2) participant is involved in a severe motor vehicle accident that precludes the participant from being able to continue on with the study, (3) participant is involved in a plane crash that results in either death or severe disability that precludes the participant from further participation in the study, (4) participant is diagnosed with a severe illness that precludes them from being able to continue further with participation in the study.

Once a study participant has stopped using the study intervention, there are no specific requirements (e.g., related to monitoring and reporting of adverse events) for follow-up since the study intervention (i.e., TARA) is considered very minimal risk by our institution's IRB.

7. SAFETY ASSESSMENTS

Participant safety will be monitored once an individual is enrolled in the study. Since our institutional IRB has deemed our TARA intervention to be very minimal risk, we do not anticipate any significant adverse experiences from our TARA intervention. However, to assure comprehensive review of potential safety events, we have included the following alphabetical list of expected adverse experiences for the TARA study intervention, criteria for management and modification of the TARA study intervention regimen or participant assessments if an adverse event occurs:

1. Experiencing difficult emotions such as sadness or anger during some of the TARA intervention class activities or home assignments. If participants experience difficult emotions, they can stop the activity and speak to the class leader or study staff. The class leader will talk about how to handle difficult emotions that come up during home assignments at the first class, and throughout the course as needed.
2. Restlessness. If participants experience restlessness, they can stop the activity and speak to the class leader or study staff. The class leader will talk about how to handle restlessness that come up during home assignments at the first class, and throughout the course as needed.

If an adverse event occurs, the AE will be assessed by Dr. Yang (medical director and co-PI) and recorded in the Adverse Event form (please see Adverse Event form in the Appendix).

7.1 Specification of Safety Parameters

To demonstrate the safety of the TARA intervention, we will carefully record all adverse events and require that < 15% of the participants experience a grade 2 (moderate) or grade 3 (severe) adverse event related to the TARA intervention.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The risk profile of our study intervention (TARA) is very minimal. Our institutional IRB has deemed our TARA study intervention to be very minimal risk. Our published peer-reviewed paper using our TARA study intervention in depressed adolescents also demonstrates the exceptional safety and very minimal risk of our TARA study intervention (Henje Blom et al., 2017). The Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters are as follows: (1) At each of the 12 study TARA intervention visits (i.e., TARA visits 1 through 12 [Study visits 2 to 13] as detailed above in section 6.1: Schedule of Evaluations), any and all adverse events will be collected and recorded using the Adverse Event form. Any Adverse Event(s) will be reviewed by the PIs and a determination of the relationship of the Adverse Event to the TARA study intervention will be made by the medical PI (Dr. Yang). Based on the study intervention relationship to the Adverse Event as determined by Dr. Yang and the severity of the Adverse Event, Dr. Yang and Dr. Tymofiyeva will decide upon the appropriate action to take regarding the study intervention (TARA).

If the Adverse Event is classified as Serious Adverse Events, the Serious Adverse Event form will be filled out.

7.3 Adverse Events and Serious Adverse Events

In the present study, an adverse event and serious adverse event will be defined as follows:

An **adverse event (AE)** will be defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events will be recorded regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** will be defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Since we do not anticipate any laboratory value changes due to the TARA study intervention, no laboratory values will be collected as part of the current protocol; thus, no laboratory values will be collected to assess safety.

Solicited adverse events will be captured in the following manner: (1) the Child Outcome Rating Scale (CORS) including the following question: "Has there been any significant unfavorable change in your mental or physical health since last class?" will be administered at every TARA session (please see Appendix. Not a source document.); (2) if the participant answers "no" to this question on the CORS, then no additional information will be requested; (3) if the participant answers "yes" to this question on the CORS and the reported event meets the definition of an adverse event given above, then the research assistant or another study staff member will ask the participant for additional details regarding the participant's answer to the CORS question and this information will be recorded in the Adverse Event form within 24 hours of the TARA study intervention session.

In order to assure that the reporting and data collection systems avoid double capture of solicited and unsolicited events, we have implemented the following items in our protocol: (1) We will ask all of the participants to report any unsolicited events in the CORS after the question, "Has there been any significant unfavorable change in your mental or physical health since the last class?"; (2) If a participant reports an unsolicited event to any of the study staff, the study staff member will ask the participant to write down this information in the CORS in order to avoid double capture of the event; (3) We also will specifically instruct our research assistants and staff to not duplicate the recording (i.e., double capture) of the same solicited and unsolicited events; (4) At the weekly clinical trial research lab meetings, the PIs (Drs. Tymofiyeva and Yang) will review with the research staff all of the CORS forms, AE and SAE forms for the prior week in order to ensure that there is no double capture(s) of any solicited and unsolicited event(s).

Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitors, and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitors, and NCCIH within 15 days of the investigator becoming aware of the problem.

All unanticipated problems will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Adverse Event Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitors, IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitors within 7 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitors, IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitors Report will state that all AEs have been reviewed.

7.4 Reporting Procedures

Please see below, Table A, for details of the reporting procedures and timelines, including the individual responsible for each step (e.g., the PIs, the Independent Monitors, etc.). The medical director, Dr. Yang (co-PI), will make the decision regarding determining the relatedness and severity of any and all AEs and SAEs. The appropriate AE and SAE forms will be completed. The completed AE and SAE forms will be sent and distributed to the appropriate individual or group of individuals (i.e.,

UCSF IRB, NCCIH) as stated below in Table A (please see below, Table A). The PIs will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. A research assistant will perform the duties of the Internal QA reviewer. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be *followed* for outcome information until resolution or stabilization.

Table A

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
Status of all enrolled subjects, as of date of reporting	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
Data entry quality control checks on 100% of charts	Weekly	QA Reviewer
Adherence data regarding study visits and intervention	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
AEs and rates (including out-of-range lab values)	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PIs, Independent Monitors NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PIs, Internal QA Reviewer
	Annually	Independent Monitors, NIH/NCCIH
Unanticipated Problems	Monthly	PIs, Internal QA Reviewer
	Per Policy	IRB

Reporting Changes in Study Status

During the funding of this study, any action by an IRB, the Independent Monitors, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Official within 3 business days of notification.

7.5 Followup for Adverse Events

The PIs will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. In the cases of adolescents with severe depression or adolescents expressing passive suicidal ideation (i.e., the adolescent expresses some potential thoughts of self-harm, but there is no intent or plan to harm herself/himself), study participants with commercial or private health insurance plans will be referred to the UCSF Langley Porter Psychiatric Institute where Dr. Yang (co-PI) sees patients, and study participants without commercial or private insurance will be referred to the UCSF Zuckerberg San Francisco General Hospital which cares for all patients regardless of their ability to pay. Participants expressing imminent suicidal ideation will be placed on an involuntary 5150 72-hour hold for danger to self by Dr. Yang. Dr. Yang is a double board certified adult as well as child and adolescent psychiatrist who sees patients at UCSF, and he is legally authorized to place an involuntary 5150 72-hour hold on the adolescent for danger to self (i.e., suicidal ideation) in order to hospitalize the adolescent if needed. The UCSF Emergency Room (ER) is located immediately adjacent to the UCSF Langley Porter Psychiatric Institute where Dr. Yang's personal clinical office and research lab are located. Following the established written protocols that are currently in place for any adolescent who expresses imminent suicidal ideation, Dr. Yang would evaluate and place an involuntary 5150 72-hour hold for danger to self on the suicidal adolescent. Dr. Yang would then contact the UCSF Langley Porter Psychiatric Institute security who are present in the building throughout the entire day and evening to help escort the suicidal adolescent to the UCSF ER. The ER physician in consultation with the on call child and adolescent psychiatrist would then evaluate the patient in the ER and decide whether to hospitalize the patient for the adolescent's safety and well-being.

7.6 Safety Monitoring

The Independent Monitoring Committee (IMC) for this study is comprised of Drs. Robert Hendren, David Becker, and Patrick Phillips. Drs. Hendren, Becker, and Phillips are not associated with this research project and work independently of the PIs, Drs. Tymofiyeva and Yang. They are not part of the key personnel involved in this grant. No member of the Committee has collaborated or co-published with the PIs within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise. Specifically, Dr. Robert Hendren, a full Professor and a Board-Certified Child and Adolescent Psychiatrist, has devoted his career to the care and research of adolescents. Dr. Hendren has exceptional expertise and extensive experience with clinical trial studies in children and adolescents. He has served on three IMCs. Dr. David Becker is a Professor of Pediatrics who specializes in integrative medicine and behavioral health. Dr. Patrick Phillips holds a PhD in medical statistics, and he has significant and extensive experience in clinical trials. (Please see the DSMP for the CVs of all members of the IMC).

8. INTERVENTION DISCONTINUATION

Participants who have met inclusion/exclusion criteria and been enrolled into the study may be discontinued if they no longer meet the study's inclusion and exclusion criteria (e.g., if the patient has started participation in another mindfulness-based intervention such as mindfulness-based stress reduction after they have enrolled into the TARA study intervention). The PIs (Drs. Tymofiyeva and Yang) will determine when criteria are met (i.e., the participant no longer meets the study's stated inclusion and exclusion criteria) for discontinuing intervention for a participant.

Possible reasons for discontinuation of the study intervention include closure by the institute (i.e., UCSF) due to significant concerns over the continued safety of the participants such as the occurrence of a natural disaster (e.g., earthquake) that renders the buildings at UCSF where the TARA study intervention is being delivered unsafe due to structural building damage arising from the earthquake.

If the TARA study intervention is discontinued for a participant (i.e., the participant no longer meets the original study entrance inclusion and exclusion criteria), the participant will be followed for one additional visit in order to allow for all of the final visit (Visit 14) assessments to be performed. Once the final visit (Visit 14) assessments are completed, the participant will no longer continue to be followed except to follow any AEs or SAEs as stated above in Section 7.4 (i.e., until 7 days [for non-serious AEs] or 30 days [for SAEs] after the last day of study participation).

A participant who has been enrolled into the study may temporary discontinue treatment if the reason for discontinuation (e.g., cold) does not preclude the participant from successfully completing the remaining study visits without missing greater than 25 percent of the 12 total TARA intervention sessions (i.e., the participant must be able to attend and complete at least 75 percent of the 12 total TARA intervention sessions) within the timeframe specified in this study (please see above, Section 6.1, Schedule of Evaluations).

While an enrolled participant is temporarily discontinued from the study intervention (e.g., cold), no additional evaluations will be performed until the participant resumes with participating in the study intervention. Once the participant resumes with participating in the study intervention, the evaluations as specified above (please see Section 6.1, Schedule of Evaluations) will then be performed based upon which session number the participant resumes her/his participation in the study.

If an enrolled participant is permanently discontinued from study intervention, then the participant will be followed for one additional visit in order to allow for all of the final visit (Visit 14) assessments to be performed. Once the final visit (Visit 14) assessments are completed, the participant will no longer continue to be followed except to follow any AEs or SAEs as stated above in Section 7.4 (i.e., until 7 days [for non-serious AEs] or 30 days [for SAEs] after the last day of study participation)..

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a randomized open-label waiting list controlled study of TARA training in 100 boys and girls aged 14-18 years. They will be individually randomized to 12 weeks of group TARA training sessions (50 to TARA training and 50 to waitlist control). The randomization is open label because there was concern that it was not possible to develop a sham training which would motivate participation and yet have no effects on the desired outcomes.

This study is designed to demonstrate that the TARA training will increase putamen connectivity (primary outcome) and decrease emotional problems on the SDQ questionnaire (secondary outcome).

Primary Hypothesis: Putamen structural node strength (primary outcome) will increase in the training group compared to controls.

S**econdary Hypothesis**: There will be a significant decrease in emotional problems measured with the Strengths and Difficulties Questionnaire (SDQ) (secondary outcome) in the training group compared to controls.

In our recent published study (Yuan et al., 2019), we demonstrated that diffusion MRI connectome methods can provide reliable and precise network measures, including the node strength, in adolescents.

The SDQ was selected because it is widely used in adolescents to measure internalizing problems and has good psychometric properties (Goodman, 2001).

For more details see section 10.3.3 Metrics.

9.2. Sample Size and Randomization

The study is powered for medium-large effect size of the meditation training on the putamen node strength. With type I error of 0.05, type II error of 0.2 (power of 80%), two-sided effect size of a Cohen's D of 0.6, the required sample size is N=45 subjects who will be studied before and after the TARA training. Given the length of the study (three months), the required commitment to participation in the training, and based on our experience, we assume an attrition rate of 10%; therefore, the target sample size is 50 subjects per group. Our primary analysis will be a general linear model of putamen node strength at week 12 with terms for baseline node strength, treatment assignment and participant sex. The primary analysis will be intent to treat and will include all randomized participants regardless of treatment receipt or protocol violations.

The only clustering in the trial will be the group delivery of the TARA intervention. We anticipate 4 TARA classes of 10-15 participants. We expect the intraclass correlation to be negligible for the following reasons: a) the TARA instructors are trained in standard procedures, b) we expect formidable individual level variation. We therefore did not include cluster assignment in the sample size calculation. We are going to test this assumption in a sensitivity analysis which extended the primary analysis by inclusion of treatment by TARA class interaction.

To standardize TARA delivery, we have included facilitator training and created a very detailed TARA manual (please see Appendix).

Treatment Assignment Procedures

We will use computer-generated randomization with variable blocks sizes of 4, 6 and 8. Individuals will be randomized with no stratification or restricted except the permuted blocks. We will permute 8 blocks of size 8, 2 blocks of size 6, and 4 blocks of size 4. The treatment assignments will be 1:1 within each block and assignments within a block will be permuted. The only masking will be in the administration of questionnaires and in the interpretation of putamen node strength.

The rationale for the use of randomization is to minimize potential biases.

The study is open label to participants, and thus there is no need for unblinding or unblinding procedures.

9.3 Definition of Populations

The intent to treat population will consist of all participants randomized into the trial regardless of treatment receipt or protocol violations.

The per protocol population will consist of all participants in the intervention group who participate in at least 75% of TARA training session plus all those in the wait list control group.

9.4 Interim Analyses and Stopping Rules

This trial will not have any interim analyses. It is itself a preliminary study which will lead to a decision about whether a follow-on study will be conducted in depressed adolescent volunteers.

Safety findings that will trigger a safety review: If 15% of the enrolled study participants experience a Grade 2 (moderate) or Grade 3 (severe) adverse event (AE) related to the TARA study intervention, then a safety review will occur.

9.5 Outcomes

The Primary Outcome and Secondary Outcomes as stated in this section (Sections 9.5.1 and 9.5.2) will be analyzed as specified in the Data Analyses section below (please see below, Section 9.6). The Primary and Secondary Outcomes will be determined based upon the data analyses as specified below in Section 9.6 which will be performed by the study statistician (Dr. David Glidden).

9.5.1 Primary Outcome

The primary outcome is putamen node strength assessed by MRI comparing the value before randomization to the one 12 weeks after randomization.

9.5.2 Secondary Outcomes

The secondary outcomes include the following:

Emotional Problems. Emotional problems will be assessed by the SDQ questionnaire comparing the value before randomization (Visit 1) to the one 12 weeks

after randomization (Visit 14).

Other outcomes

Adherence. The proportion of volunteer randomized to TARA training who participate in at least 75% of the sessions. We expect that at least 80% of participants on the TARA arm will attain this level of adherence.

Safety and tolerability of the intervention. Adverse events will be collected at each visit and graded, and their attribution to their participation will be assessed**.** The safety of the TARA intervention will be demonstrated if < 15% of the participants experience a grade 2 (moderate) or grade 3 (severe) adverse event related to the TARA intervention.

To demonstrate the tolerability of the intervention used in this study, we will use the Child Session Rating Scale (CSRS) score. The CSRS is a 4-item self-assessments using a 10-cm visual analog scale (Campbell & Hemsley, 2011), with higher scores indicating better experience. This measure of tolerability will be completed after each session. Participants will rate the session in terms of how much they felt listened to, how important the content and activities were to them, how much they liked the session, and their overall experience. The intervention will be tolerable if the median CSRR is at least 20 in >80% of participants.

Retention. To demonstrate the ability to retain subjects, we will retain at least 80% of randomized participants for primary outcome measurement at the end of the study regardless of adherence to the intervention.

9.6 Data Analyses

Primary Outcome. To attain the primary objective, we will test the hypothesis that an increase in the node strength of the putamen (dependent variable) will be observed in the training group compared to the controls. This hypothesis will be tested using an analysis of covariance (ANCOVA) accounting for sex and fit by maximum likelihood. Stata (College Station, TX) will be used to perform data analyses. The use of maximum likelihood mitigates susceptibility to missing data. Examination of variable distribution and outlier identification will be performed. We will additionally explore age, pubertal status (as determined by the Tanner stage self-report form (Tanner et al., 1962)), and pre-training associations with the changes through an examination of interaction. Potential pre-/post-training differences in movement during MRI will be accounted for by assessing the number of rejected diffusion directions. **Sex as a biological variable:** In all analyses described, sex will be included as a factor, we will also test for a randomized arm by sex interaction.

The only clustering in the trial will be the group delivery of the TARA intervention. We anticipate 4 intervention arm clusters of 10-15 participants. We expect the intraclass correlation to be negligible for the following reasons: a) the TARA instructors are trained in standard procedures, b) we expect formidable individual level variation. We are going to test this assumption in a sensitivity analysis which extended the primary analysis by inclusion of treatment by TARA class interaction. We are going to test this assumption in a sensitivity analysis which extended the

primary analysis by inclusion of treatment by TARA class interaction.

To standardize TARA delivery, we have included facilitator training and created a very detailed TARA manual (please see Appendix).

In addition, we will examine relationship between changes in node strength of the putamen and adherence to sessions, proportion of sessions attended, by performing a Spearman rank correlation of TARA adherence (by percentage of sessions attended) and change in node strength. We will use ANCOVA analysis with a treatment by attendance interaction to estimate the putamen node strength which would be achieved with full attendance in all training session.

Secondary Outcome.

Emotional Problems. Our hypothesis is that training will improve emotional problems as assessed by the SDQ T-score compared with controls. We will use an analysis of covariance (ANCOVA) accounting for sex and fit by maximum likelihood. Stata (College Station, TX) will be used to perform data analyses. We will additionally explore age, pubertal status (as determined by the Tanner stage self-report form (Tanner et al., 1962)), and pre-training associations with the changes through an examination of interaction. Potential pre-/post-training differences in movement during MRI will be accounted for by assessing the number of rejected diffusion directions. **Sex as a biological variable:** In all analyses described, sex will be included as a factor, we will also test for a randomized arm by sex interaction.

In addition, we will examine relationship between changes in node strength of the putamen and changes in emotion by performing a Spearman rank correlation change in node strength through 12 weeks with change in SDQ through 12 weeks.

Other outcomes.

Adherence. We summarize adherence to training including (i) tabulating the number of participants on the training arm who complete at least 75% of sessions, (ii) calculate the minimum, maximum, median and interquartile range of sessions attended by those randomized to the TARA training arm.

Safety and tolerability of the intervention. Adverse events of grade 2 or higher will be tabulated between the arms and compared by the Fisher exact test. Tolerance scores on the CSRS will be summarized (minimum, maximum, median, interquartile range) at each study visiting on the TARA training arm.

We will tabulate the proportion of participants who are retained through 12 weeks and complete the MRI exam and SDQ questionnaire. These will be compared between the arms by the Fisher exact test.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Information for each participant will be collected using the following forms and procedures:

- Informed Consent Form (will be obtained and signed by RA via DocuSign)
- Medical History Form (source document, will be collected and signed by RA via DocuSign)
- Inclusion/Exclusion criteria form (source document, will be filled out and signed by RA via DocuSign)
- Enrollment/Randomization form (source document, will be filled out and signed by RA via DocuSign)
- MRI screening form (will be signed by the MRI technician. Not a source document.)
- MRI brain scan (will be performed using a 3T MRI scanner)
- Demographics assessment (will be performed electronically in Qualtrics)
- SDQ assessment (will be performed electronically in Qualtrics)
- Baseline Visit Checklist (source document, will be filled out and signed by RA via DocuSign)
- Child Session Rating Scale (CSRS) (source document, will be collected and signed by RA)
- Child Outcome Rating Scale (CORS) including the question: "Has there been any significant unfavorable change in your mental or physical health since last class?" (will be collected by RA. Not a source document.)
- Adverse Events (source document, if the answer is Yes to the question above in CORS, this form will be filled out and signed by RA via DocuSign)
- Serious Adverse Events (source document, if answered Yes to the SAE question in the Adverse Event form, this form will be filled out by RA, signed by PI via DocuSign)
- On Study Visit Checklist Form (source document, will be filled out and signed by RA via DocuSign)
- Study Completion form (source document, will be filled out by RA, signed by PI via DocuSign).

All source documents will be signed and stored electronically in DocuSign. Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All computer entry and networking programs will be done

using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by the UCSF IRB, the NCCIH, and the OHRP.

10.2 Data Management

It is a single-site study; therefore, the site of operation and the Data Management Center are the same site. All the data collection described in the previous section, as well as the statistical analysis of the data will take place at UCSF.

The data collection forms that will be used in the present study are listed and described above (please see Sections 6.1, 6.2, 6.2.2, 6.2.4, 6.2.5, and 7.3).

10.3 Quality Assurance

10.3.1 Training

RAs will be training directly by the study PIs, who will also be available for questions. Dr. Eva Henje Blom will conduct annual teacher training for the facilitators of TARA and monitor treatment fidelity using the 10-item fidelity scale (Clarke, 1998), as described in the section 10.3.5. Monitoring below.

10.3.2 Quality Control Committee

In addition to the Independent Monitor Dr. Hendren, one of the RAs will be appointed as the Internal QA Reviewer.

The reports that Dr. Hendren will review are specified above in Table A (please see Section 10.3.5 below, Table A).

10.3.3 Metrics

Primary outcome measure: Putamen structural node strength. In our recent published study (Yuan et al., 2019), we demonstrated that diffusion MRI connectome methods can provide reliable and precise network measures, including the node strength, in adolescents.

Secondary outcome: Emotional problems measured with the Strengths and Difficulties Questionnaire (SDQ). The SDQ was selected because it is widely used in adolescents to measure internalizing problems and has good psychometric properties (Goodman, 2001).

10.3.4 Protocol Deviations

The PIs will use the NCCIH Protocol Deviation Tracking Log form (see Appendix) with the following protocol deviation code, to monthly record any and all protocols deviations.

Protocol Deviation Codes:

A – Consent Procedures

B – Inclusion/Exclusion Criteria

C – Concomitant Medication/Therapy

D – Laboratory Assessments/Procedures

E – Study Procedures

F – Serious Adverse Event Reporting/Unanticipated Adverse Device Effect

G – Randomization Procedures/Study Drug Dosing

H – Visit Schedule/Interval

I – Efficacy Ratings

J – Other

Protocol deviations will be recorded in the tracking log as they occur, to ensure completeness and accuracy of the data.

For each deviation the PIs will determine whether the deviation meets IRB and NCCIH reporting requirements.

The PIs will sign each form after it has been completed or immediately prior to a monitoring visit. If it has been signed with fewer than five deviations entered into it, the next identified deviation will be reported on a new page to ensure that all deviations have been reviewed by the PIs.

Each page will be numbered, and the log will be maintained in the Essential Documents Binder, behind the Protocol Deviations tab. The pages will be stored in reverse chronological order, with the newest pages of the log placed at the front of the section. At the conclusion of the study, the final page of the log will be identified by checking the box in the footer.

10.3.5 Monitoring

In addition to the Independent Monitors, one of the RAs will be appointed as the Internal QA Reviewer. The monitoring of protocol compliance and data quality will be conducted in accordance with Table A below.

Table A

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
Status of all enrolled subjects, as of date of reporting	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
Data entry quality control checks on 100% of charts	Weekly	QA Reviewer
Adherence data regarding study visits and intervention	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors
AEs and rates (including out-of-range lab values)	Monthly	PIs, Internal QA Reviewer
	Semi-annually	Independent Monitors

	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PIs, Independent Monitors NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PIs, Internal QA Reviewer
	Annually	Independent Monitors, NIH/NCCIH
Unanticipated Problems	Monthly	PIs, Internal QA Reviewer
	Per Policy	IRB

In addition to the monitoring described in Table A above, Dr. Henje Blom will monitor treatment fidelity using the 10-item fidelity scale (Clarke, 1998). For that purpose, all group sessions will be audio-recorded; the research consent process will include consent to audio record groups to facilitate treatment fidelity coding. A random sample (20%) of group sessions will be rated by Dr. Henje Blom for adherence to the training manual and facilitator competence using the 10-item fidelity scale.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (please see Appendix) and any subsequent modifications will be reviewed and approved by the UCSF IRB committee responsible for oversight of the study. The consent form is separate from the protocol document and included in the Appendix. Two versions of consent form are available: for 14-17-year-old participants and for 18-year-old participants.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those who are under the age of 18 years (e.g., minor), the parent or legal guardian of the participant who is a minor must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. An electronic DocuSign copy will be given to each participant who is at least 18 years old and to the parent or legal guardian for each participant who is under 18 years old, and this fact will be documented in the participant's record. Participants 18 years old will sign the consent forms themselves since they are legally considered adults.

11.3 Participant Confidentiality

Any data, forms, reports, video recordings, and other records that leave the site will

be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet located within a locked room that is within a locked building with 24 hours security surveillance cameras and 24 hours security personnel guarding and patrolling the locked building to ensure that the records will be kept safe and not stolen. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by the UCSF IRB, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the UCSF IRB, the NCCIH, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

The current study does not have any committees.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the co-PIs of the present study (Drs. Tymofiyeva and Yang). We will disseminate the results from this research as broadly as possible.

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15. SUPPLEMENTS/APPENDICES

- Phone Pre-Screening of Inclusion/Exclusion Criteria
- Informed Consent Form for 14-17-year-old participants
- Informed Consent Form for 18-year-old participants
- Medical History Form
- Inclusion/Exclusion Criteria Form
- Enrollment/Randomization Form
- MRI Screening Form
- SDQ questionnaire
- Demographics questionnaire
- Baseline Checklist Form
- CORS
- CSRS
- On Study Visit Checklist
- Adverse Events Form
- Serious Adverse Events Form
- Study Completion Form
- Protocol Deviation Tracking Log
- TARA manual