

Study Protocol

Official Title:

Anhedonia, Development, and Emotions: Phenotyping and Therapeutics (ADEPT)

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Scientific Background

Anhedonia—difficulties with reward-focused motivation, anticipation, and effort—predicts poor treatment response and pernicious clinical course in people with depression. A core symptom that also anchors a subtype of depression, anhedonia often precedes the emergence of serious psychopathology, increases risk for suicidality, and reduces the likelihood of responding to pharmacologic or psychosocial treatment (McMakin et al., 2012; Rizvi et al., 2016).

Adolescence to young adulthood is the optimal developmental point for investigating anhedonia in order to improve treatment outcomes. Adolescence is a period of vulnerability for anhedonia, possibly through convergence of changes in frontostriatal reward, dopamine (DA), and reward-related behavioral systems. Anhedonia and depression both begin during adolescence, perhaps not coincidentally during the development of anhedonia's putative neural substrate, the frontostriatal reward system. This neurobehavioral shift, in combination with an early stage in the clinical course of depression, creates an opportunity during adolescence and early adulthood to understand and potentially change the influence

of anhedonia.

The development of anhedonia could reflect diminished DA availability, undermining frontostriatal reward integration and resulting in the persistence of depression or related changes in mood and behavior.

DA can be measured non-invasively by MRI proxy. Brain tissue iron is critical for DA synthesis (Ortega et al., 2007; Zucca et al., 2017), is predominant in the basal ganglia (Haacke et al., 2005), increases through early adulthood (Larsen & Luna, 2018; Peterson et al., 2019), is associated with PET indices of DA availability (Larsen et al., 2020), mediates developmental specialization of frontostriatal functional connectivity through adolescence (Parr et al., 2021), and can be measured non-invasively with MRI. Three indirect indices of DA availability depend on brain tissue iron: R2' is linearly related to striatal tissue iron (Sedlacik et al., 2014), which co-localizes with DA vesicles (Larsen et al., 2020); T2* is a relative measure of tissue iron that can be obtained from fMRI; Neuromelanin (NM) is the pigment that indicates density of nigrostriatal DA neurons (Sulzer et al., 2018; Cassidy et al., 2019).

Inflammation is associated with anhedonia and depression, perhaps particularly in adolescence, and is postulated to exert its influence through changes in striatal dopamine and function in frontostriatal reward circuitry. The relation of inflammation to depression, including in adolescents, is widely documented (Mitchell & Goldstein, 2014), with anhedonia postulated as a specific neuroinflammation-related symptom (Miller & Raison, 2016). Low striatal DA availability and signaling are considered a key mechanism of the inflammation-depression association (Felger & Treadway, 2017). The immune system undergoes considerable development during adolescence (Osugi et al., 1995), with putative consequences for anhedonia (Brenhouse & Schwarz, 2016).

Assessing positive affect, social experiences, sleep, and symptoms in real life and real time provides rich, powerful information on how anhedonia operates in relation to functioning. Beyond the traditional, retrospective, lab-based measures of anhedonia, techniques to measure real-life experiences and behavior using smartphone apps provide greater temporal, featural, and contextual precision that will advance understanding of anhedonia. Social experiences reveal the consequences of anhedonia for functioning, and sleep is critical to affect regulation.

TBS to dmPFC holds promise for reducing anhedonia and improving clinical course in young people with depression. In contrast to the long-duration,

dorsolateral prefrontal cortex-focused TMS approach to depression, we have used TBS—a briefer and more easily tolerated form of TMS—to dmPFC, a target in frontostriatal reward circuitry. Based on our findings and the literature (e.g., Forbes & Dahl, 2012), our guiding hypothesis is that youth with depression exhibit excessive dmPFC response, which serves to dampen VS responding. Thus, our goal is to reduce dmPFC activity through continuous TBS.

PA Training is a psychosocial add-on intervention that could enhance the effects of TBS. PA Therapy (Craske et al., 2016) is an innovative cognitive and experiential technique developed to address anhedonia specifically and, ideally, change altered patterns of frontostriatal function. Standing in contrast to Cognitive Behavioral Therapy, PA training has efficacy for enhancing positive affect and reducing negative affect (Craske et al., 2018). This treatment can be easily applied, and we propose that it will enhance neural circuit-level changes elicited by TBS.

Examining the development of anhedonia can provide critical knowledge about its role in the course and severity of depression, its influence on healthy functioning, and the functional consequences of disrupting its influence with therapeutic approaches involving neuromodulatory, cognitive-behavioral, and pharmacologic techniques. This developmental focus will provide a foundation for optimal treatment assignment, development of more effective treatments, and the opportunity to put young people on a path toward resilience and thriving.

The innovation of the study lies in its strategy for capturing anhedonia, manipulating its mechanisms, and trying to improve the clinical profile of young people who experience it. The features that make it innovative and high-impact include its longitudinal examination of early anhedonia; use of a frontostriatal rather than a dorsolateral PFC target, compressed schedule, and theta burst for TMS; addition of PA Therapy-based cognitive-behavioral exercises to TBS; non-invasive measurement of DA availability; and multi-modal investigation of anhedonia (across neuroimaging, neuromodulation, cutting-edge pharmacotherapy, immunology, ambulatory experience sampling and sensor technology, and sophisticated computational techniques).

Study Objectives

Goal 1. Uncover the complex nature of anhedonia using high dimensional, multi-modal data that captures neural, behavioral, and experiential mechanisms in adolescents and young adults with depression. We will focus on function in neural

reward circuitry using resting and task fMRI; dopamine (DA) availability using MRI; inflammatory markers; ecological momentary assessment (EMA) of mood, social experiences, and symptoms; and sensor technology to assess motor activity, location (e.g., proportion of time spent at home), sleep/wake patterns, and social context (e.g., isolation). Machine learning techniques will compute digital phenotyping, cross-method computational phenotyping, and clustering profiles. The hypothesis is that anhedonic depression is characterized by disrupted frontostriatal function, low dopamine availability, altered inflammatory markers, low activity level, and social isolation. In addition, phenotypes based on this combination of methods will be detectable.

Goal 2. Manipulate the neural mechanisms of anhedonia using 3 treatments found to improve anhedonia, putatively through influence on frontostriatal function. These are (1) continuous theta burst stimulation (cTBS), a form of transcranial magnetic stimulation, to dorsomedial prefrontal cortex (dmPFC); (2) positive affect (PA) exercises drawn from a psychosocial treatment shown to improve PA and treat depression. All participants will receive a 20-session (2/day), 2-week course of cTBS targeting frontostriatal reward circuitry. With a brain target related to anhedonia, more dense schedule, and briefer administration than standard transcranial magnetic stimulation (TMS) for depression, we will attempt to improve anhedonia and depression by reducing (1) high dmPFC function, which we have found is associated with adolescent anhedonia (Healey et al., 2014) and (2) dmPFC dampening of ventral striatal (VS) response. Participants who receive TBS will receive PA exercises drawn from PA Therapy (Craske et al.). Outcomes will include anhedonia phenotypes computed in Goal 1, as well as traditional clinical variables and brain function.

Goal 3. Conduct sophisticated analytics to examine the association of computational phenotypes of anhedonia with device/pharmacologic response, clinical course, and functioning over 1 year. To connect the descriptive analytics of Goal 1 with treatment response (Goal 2), development, and clinical course, we will use machine learning techniques with our high-dimensional, integrative, multi-modal data to examine predictors of response to TBS and the relation of biological, digital, and clinical factors in the persistence of anhedonia and its phenotypes. We will also be able to test other questions, including within-person pathways to healthy functioning; prescriptive analytics to consider how to assign to TMS; change point analyses for fluctuation in anhedonia after treatment; and contributions to worsening or improvement of anhedonia over 1 year.

Study Design & Methods

The study has a longitudinal design in which participants complete 2 sets of activities:

Phase 1: Phenotyping. This includes assessment with diagnostic interview, questionnaires, behavioral tasks, MRI, app-based digital assessment, and blood draw for inflammatory markers. These activities will occur at 4 time points over the course of 1 year/participant (study entry, approximately 4 months, approximately 5 months, and approximately 1 year), and all participants will complete them.

Phase 2: Therapeutic activities: 20 theta burst stimulation (TBS) sessions for all participants and 10 sessions of either positive affect (PA) training or control training.

This design allows the phenotyping and description of anhedonic depression; the prediction of response to treatment; the computation of prescriptive treatment assignment retrospectively; and the detection of changes in phenotype and component characteristics (e.g., functional connectivity of reward circuitry) in relation to treatment, development, and time. Ultimately, the knowledge gained will inform the prevention and treatment of anhedonic depression by taking a clinical neuroscience approach to understanding this condition, its mechanisms, and its improvement with treatment.

The primary endpoints are anhedonia severity and depressive disorder. The secondary endpoints include frontostriatal circuit function, DA availability, peripheral inflammation, reward behavior, subjective positive affect, locomotion and motor activity, sleep characteristics, and phenotype severity/group.

The ADEPT Study will be divided into 2 Phases, with phenotyping in Phase 1 and therapeutics in Phase 2. Phase 1 includes MRI, blood draw for inflammatory markers, behavior tasks, diagnostic interviews, questionnaires, and phone-based EMA and sensor data collection activities. Phase 2 includes TBS and PA training. All participants will complete both phases.

1. Eligibility - both Phases:

At the eligibility visit for Phase 1, participants will complete written informed consent; the SCID-5 to diagnose DSM-5 disorders; the MADRS to assess depression severity; the SHAPS to assess anhedonia; a medical history form; and a treatment

history form. The eligibility visit may be broken into two or three parts as needed, and some procedures may be conducted virtually as appropriate.

For Phase 2, participants will complete self-report measures of health relevant to TMS, a urine drug screen, and a urine pregnancy test (for those assigned female at birth). For Phase 2 participants, the visit to the M-CTRC lab at the time point after TMS will include vital signs, urine drug screen, urine pregnancy screen, and ECG. The PI or proxy (i.e., co-investigator or study physician) will review materials for eligibility and sign to confirm. Medical findings will be reviewed by a board-certified physician co-investigator prior to the TMS procedures.

Once informed consent for phase 2 has been completed, a consult with a study physician will occur, in which the physician will determine whether TMS treatment would be appropriate for the participant. If TMS is not deemed appropriate, the participant will not continue in the study.

Eligibility procedures may be ended early if it is clear that a participant does not meet inclusion/exclusion criteria (eg., participant reports taking an exclusionary medication).

2. Interview and Questionnaires - Phase 1:

Participants will complete SCID diagnostic interviews at study entry. Also at study entry, the affect induction tasks will be completed (5-10 minutes) which involves a conversation with the participant and comparing vocal data. Participants will complete the MADRS interview on depressive severity and the SHAPS questionnaire on anhedonia severity at study entry, pre/post-TMS, and at 1 year. Interviews may be conducted in person or by HIPAA-compliant zoom virtual format.

At 4 time points, participants will complete other self-report questionnaires. These time points are at entry, and approximately at month 2-4 (after TBS), month 4-6, and 1 year. Questionnaires assess symptoms, demographic characteristics, and relevant experiences (e.g., trauma history).

3. MRI - Phase 1:

At the first 2 time points above, participants will complete a 1.5-hour (scan 1-2) or a 1-hour scan (scan 3) at the CMU Bridge Center or Presby MRRC. The MRI visits will involve 2 resting state MRI scans, a guessing reward fMRI task in which participants can win money, scans to assess striatal tissue iron and midbrain neuromelanin, and a structural scan. Scans 1-2 will also include an fMRI task

involving effort to obtain reward, if participant interest and time limits allow. The tissue iron and neuromelanin scans will be used to compute proxy variables for dopamine availability, allowing measurement of dopamine function in reward circuitry. Participants can expect these visits to take approximately 1.5 hours (2.25 hours if effort task is included).

4. Inflammatory Markers - Phase 1:

At the first 2 time points (described above), participants will complete a 30mL blood draw. Venipuncture will be conducted by a phlebotomist at the WPH phlebotomy lab. The venipuncture procedure will be billed to study accounts and not to participants or their insurance.

5. Behavior - Phase 1:

At the first two time points as above, participants will complete behavior tasks that are presented by computer and assess reward processing.

6. Digital phenotyping - Phase 1:

For approximately the first 6 and last 3 months of participation in the study, participants will complete an ecological momentary assessment (EMA) procedure with collection of self-reported mood, symptoms, and related experiences (e.g., sleep quality) for 7-day bursts, with one burst per month. EMA will occur by phone, using app, such as EARS or WDX, text, or browser, to present surveys and collect data. Data will be encrypted, protected, and stored using HIPAA-compliant techniques.

For the entire year of participation in the study, the EARS app may collect data from phone sensors to determine variables related to anhedonia, such as motor activity (from accelerometer) and location (from GPS). Data will be encrypted, protected, and stored using HIPAA-compliant techniques.

7. Computer Cognitive Tasks:

After the first and second Phenotyping Visits, participants will complete computer tasks remotely (approx. 1 hour). They will receive a link by email and will complete the tasks when convenient for them. The tasks will include an effort-based reward task in which participants make decisions about pressing a button to obtain small or large rewards and a task in which participants go through learning and unlearning using aversive stimuli (a scream sound). A questionnaire will be in the middle of the two tasks. This questionnaire serves as a break to separate the acquisition and extinction phases, which is important for the task to be realistic and valid, and data will not be collected from the questionnaire.

8. Theta Burst Stimulation (TBS) - Phase 2:

Participants in Phase II of the study will undergo 2 sessions of continuous TBS (cTBS) per day over 10 days (on weekdays, over 2 weeks; 20 sessions total). TBS is a form of TMS. TBS will be conducted by research personnel who have undergone comprehensive training according to the SOP previously provided to the IRB for STUDY20050081.

TBS will be administered with the MagPro X100 Transcranial Magnetic Stimulation (TMS) system, which is FDA cleared for Theta Burst Stimulation (TBS) treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode (k170114, k150641, and k171481). Thus, the device is acceptable for use in this research context.

The total time of each pair of sessions will be approximately 1 hour, with each administration of TBS lasting approximately 2 minutes. Before the first TBS session on each TBS session day (i.e., 10x during the study), participants will be asked "How well did you sleep last night?" Additionally on each TBS session day, participants will complete self-report forms on recent substance use and medical status. If drug use or change in medical status is reported, a team member will assess for such change and contact a study MD as needed (e.g., participant has started a new medication) to determine whether the participant can continue to receive TBS. At the beginning and end of each TBS visit (once for every pair of TBS sessions, or 10x total), participants will rate their pain levels. After all TBS sessions have been completed, participants will complete an acceptability scale. Participants can miss up to two consecutive days of TMS as long as they come for the appropriate total number of visits.

9. PA training - Phase 2:

At each TBS visit, participants in Phase II will complete a positive affect (PA) training task (30-45 min per training session). The exercises in the PA training are designed to enhance reward processing and PA, and they will be adapted from Positive Affect Therapy, a psychosocial treatment targeting anhedonia and intended to improve disrupted frontostriatal function (Craske et al., 2016). This treatment reduces negative affect and enhances PA (Craske et al., 2018). PA training will be administered by trained research staff.

10. Follow-up assessment - Phase 1:

The follow-up assessment approximately 1 year after entering the study will include

the MADRS and questionnaires described above. The participant will also complete the study completion survey.

Eligibility Criteria

Inclusion criteria are as follows:

Phase 1 (all participants)

- Age 15-25
- Current DSM-5 depressive disorder
- Severity ≥ 12 on MADRS
- Moderate-severe anhedonia (75% of sample) or low anhedonia (25% of sample)

Phase 2 (for participants in TBS phase, in addition to above)

- ≥ 1 failed antidepressant trial (for qualification for Phase 2 of study and definition of non-response to TMS to be eligible for ketamine) = Treatment for at least 6 weeks with an antidepressant medication reaching recommended dosage for adults for at least 3 weeks of the treatment (e.g., 20 mg fluoxetine)

Exclusion criteria are as follows:

Phase 1 (all participants)

- Lifetime psychosis, bipolar disorder, autism spectrum disorder, or developmental disorder
- Serious, unstable neurological disorder (e.g., seizure disorder)
- Brain injury with loss of consciousness
- Moderate-severe substance use disorder, past 6 mos.
- MRI contraindications (e.g., claustrophobia or ferromagnetic objects that cannot be removed from the body, weight > 300 lbs)

Phase 2 (for participants in TBS phase, in addition to above)

- Serious, unstable respiratory or cardiovascular illness
- Pre-TBS: Alcohol binge in past week, which is defined as the number of drinks over a two-hour period greater than or equal to: 4 drinks for women, 5 drinks for men, 3 drinks for girls (15-21) and 4 drinks for boys (ages 15-21).
- Pre-TBS: Current illicit stimulant use
- Pregnancy
- High blood pressure
- Lifetime recreational ketamine or PCP use
- Lifetime history of seizure

Statistical Considerations

Analyses will test pre-/post-treatment change in severity of depression symptoms (from MADRS) and anhedonia symptoms (from SHAPS) using repeated measures tests. Change in symptoms will be computed in separate models for TMS+PAT and for TMS+PAT, then ketamine, and for depression and anhedonia. Given the small number of tests, there will not be additional correction for Type I error, and statistical threshold for each test will be set at $p < .05$. For statistical power, G*Power 3.1 tests indicate that for repeated measures models with the original target sample of 100 participants, we will have >95% power to detect change in symptoms with medium effect size of $f=.0.2$.