

**Reducing Suicide Risk in Adolescents and Young Adults via a Psychobehavioral Intervention to
Regularize Daily Rhythms and Improve Brain Circuitry Functioning**

Protocol Version

8/27/24

Version:9

Clinical Trials Registration Number (if applicable): NCT05317481

Synopsis**Purpose**

The purpose of this study is to advance a non-pharmacologic suicide preventive intervention with wide dissemination potential as an innovative high-yield solution to reduce suicide rates. We aim to achieve this with this study of Brain Emotion Circuitry Self-Monitoring and Regulation Therapy for Daily Rhythms (BE-SMART-DR), a modification of Social Rhythm Therapy (SRT) that provides self-directed strategies to regularize sleep and other DRs to reduce short-term suicide risk that can be used lifelong to potentially also reduce long-term suicide risk.

Please note: the methods of this study are largely the same as in our currently approved HIC protocol 0407026910. This new protocol is for an expanded study with new funding from the American Foundation for the Prevention of Suicide. The main difference is we may exclude more lower risk subjects who have never had any suicidality, and that there is a psychoeducational control condition subjects can be randomized to, but we will be including similar subjects, methods are largely similar, and as in 0407026910 the intervention will be administration in addition to current treatment in the community and no subject will be asked to stop any treatment in the community.

Objectives

- 1) Show pre-post BE-SMART-DR suicidal ideation and propensity (SI/P) decreases associated with DR regularity and quality increases
- 2) Show pre-post BE-SMART-DR improvements in the functioning of a brain system that subserves emotional and other behavioral control (i.e., a hypothalamus-amygdala-ventral prefrontal cortex (vPFC), (HAV), system)

Study Population

We plan to study adolescents and young adults with diagnostic and statistical manual of mental disorders 5 (DSM5) diagnoses of bipolar disorder (BD) I, II or Otherwise Specified (OS) or major depressive disorder (MDD), as they have been shown to have HAV system dysfunction and high suicide rates, and there is preliminary evidence that BE-SMART-DR has beneficial effects on the brain and in reducing suicide risk in this population.

Number of Participants

We plan to enroll 128 (estimating 25% attrition to 96 completers) participants based on statistical power analysis.

Study Design

This is a randomized control trial (RCT) with blind subjects randomized 2:1 (using block randomization) to BE-SMART-DR or a psychoeducational control comparator condition (CC). Participation will include research clinical/behavioral interviews and symptom self-ratings, magnetic resonance imaging (MRI) scanning, actigraphy wearables, and use of MetricWire app on smartphones for ecological momentary assessment (EMA). Subjects randomized to BE-SMART-DR will participate in 12 weekly sessions with a research therapist with the first, middle and last sessions in person, remaining sessions offered by secure video or audio telecommunication and 6-month in person follow-up. Subjects randomized to the CC will participate in 12 weekly sessions consisting of watching pre-taped videos facilitated by a research coordinator with the first and middle in-person visits, and with the last session done in person with their study coordinator. Subjects will participate in a total of three MRI scans on their in-person visits excluding the 6-month follow-up.

Study Duration

For each subject: about 9 months (12 weekly session and re-assessments 6-months after 12 weekly session completion).

Overall research project: anticipated to be at least 3 years.

Outcome Variables

The primary outcome variables include for SI/P the Beck Scale for Suicidal Ideation (SSI) and Concise Health Risk Tracking (CHRT) scale, for DR regularity and quality the social rhythm metric (SRM), brief social rhythm scale (BSRS) and Pittsburgh Sleep Quality Inventory (PSQI) and for brain functioning functional MRI (fMRI) measures of the HAV.

Locations/Facilities

Mood Disorders Research Program, 60 Temple St. Suite 6B and
Magnetic Resonance Research Center at the Anlyan Center, 300 Cedar Street

Abbreviations

Abbreviation	Explanation
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AE	Adverse Event
ASRM	Altman Self-Rating Mania Scale
BD	Bipolar Disorder
BE-SMART-DR	Brain Emotion Circuitry Targeted Self-Monitoring and Regulation Therapy for Daily Rhythms
BHI	Beck Hopelessness Scale
BIS	Barratt Impulsiveness Scale
BSRS	Brief Social Rhythm Scale
CASA	Child and Adolescent Services Assessment
CC	Control Comparator Condition
CHRT-SR	Concise Health Risk Tracking Scale – Self Report
CSHF	Columbia Suicide History Form
CSQ	Client Satisfaction Questionnaire
C-SSRS	Columbia Suicide Severity Rating
CTQ	Childhood Trauma Questionnaire
DERS	Difficulties in Emotion Regulation Scale
DISP	Diagnostic Interview for Sleep Patterns and Disorders
DR	Daily Rhythm
DSM5	Diagnostic and Statistical Manual 5
DSMP	Data Safety Monitoring Plan
EHI	Edinburgh Handedness Inventory
EMA	Ecological Momentary Assessment
ERS	Emotion Reactivity Scale
FHE	Family History - Epidemiology
fMRI	Functional Magnetic Resonance Imaging
HAV	Hypothalamus-Amygdala-Ventral Prefrontal
HDRS	Hamilton Depression Rating Scale
HSPT	Human Subject Protection Training
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia -Present and Lifetime
LAR	Legally Authorized Representative
MCQ	Munich Chronotype Questionnaire
MLS	Medical Lethality Scale
MDD	Major Depressive Disorder
MDRP	Mood Disorders Research Program

mMARCH	Motor Activity Research Consortium for Health
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
OS	Otherwise Specified
PDS	Pubertal Development Scale
PFC	Prefrontal Cortex
PHI	Protected Health Information
PI	Principal Investigator
PMAS	Promis Medication Adherence Scale
PSQI	Pittsburgh Sleep Quality Index
QIDS-SR	Quick Inventory of Depression Symptomology-Self Report
RCT	Randomized Clinical Trial
SA	Suicide Attempt
SAE	Serious Adverse Event
SAFE-T	Suicide Assessment Five-Step Evaluation and Triage
SCID-5 PD	Structured Clinical Interview for DSM-5 Personality Disorder
SCID-5 RV	Structured Clinical Interview for DSM-5-Research Version
SES	Socioeconomic Status
SI	Suicidal Ideation
SI/P	Suicidal Ideation/Propensity
SRM	Social Rhythm Metric
SRT	Social Rhythm Therapy
SSI	Scale for Suicide Ideation
STBs	Suicidal Thoughts and Behaviors
UP	Unanticipated Problem
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
vPFC	Ventral Prefrontal Cortex
WASI	The Wechsler Abbreviated Scale of Intelligence
YMRS	Young Mania Rating Scale

Protocol Revision History

Version Date	Summary of Substantial Changes
12/13/22	Adding MetricWire App and their research portal for our EMA

Table of Contents

<u>Preface</u>	1
<u>Synopsis</u>	2
<u>Purpose</u>	2
<u>Objectives</u>	2
<u>Study Population</u>	2
<u>Number of Participants</u>	2
<u>Study Design</u>	2
<u>Study Duration</u>	2
<u>Outcome Variables</u>	3
<u>Locations/Facilities</u>	3
<u>Abbreviations</u>	3-4
<u>Protocol Revision History</u>	5
<u>1 Background</u>	6
<u>1.1 Background</u>	6
<u>1.2 Prior Experience (if applicable)</u>	8
<u>2 Rationale/Significance</u>	8
<u>2.1 Rationale and Study Significance</u>	8
<u>2.2 Risks</u>	8
<u>2.3 Anticipated Benefits</u>	10
<u>3 Study Purpose and Objectives</u>	10
<u>3.1 Purpose</u>	10
<u>3.2 Hypothesis</u>	10
<u>3.3 Objectives</u>	10
<u>4 Study Design</u>	11
<u>4.1 Study Duration</u>	12
<u>4.2 Outcome Variables/Endpoints</u>	12
<u>4.2.1 Primary Outcome Variables/Endpoints</u>	12
<u>4.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable)</u>	13
<u>5 Study Participants</u>	13
<u>5.1 Study Population</u>	13
<u>5.2 Number of Participants</u>	13
<u>5.3 Eligibility Criteria</u>	13
<u>5.4 Recruitment Procedures</u>	13
<u>5.5 Consent/Assent Procedures/HIPAA Authorization</u>	14
<u>6 Study Methods/Procedures</u>	14
<u>6.1 Study Procedures</u>	14
<u>6.1.1 Data Collection</u>	18
<u>6.2 Method of Assignment/Randomization (if applicable)</u>	19
<u>6.3 Adverse Events Definition and Reporting</u>	19
<u>6.4 Reaction Management</u>	19
<u>6.5 Withdrawal Procedures</u>	19
<u>6.6 Locations/Facilities</u>	20
<u>7 Statistical Design</u>	20
<u>7.1 Sample Size Considerations</u>	20
<u>7.2 Planned Analyses</u>	20
<u>7.2.1 Secondary Objective Analyses (if applicable)</u>	21
<u>7.2.2 Analysis of Subject Characteristics (if applicable)</u>	21
<u>7.2.3 Interim Analysis (if applicable)</u>	21
<u>7.3 Data Relevance</u>	21
<u>7.4 Data Coding</u>	21

7.5	<u>Data Analysis Tools</u>	21
7.6	<u>Data Monitoring</u>	21
7.7	<u>Handling of Missing Data</u>	21
8	<u>Data/Specimen Handling and Record Keeping</u>	22
8.1	<u>Subject Data Confidentiality</u>	22
8.2	<u>Data Quality Assurance</u>	22
8.3	<u>Data or Specimen Storage/Security</u>	22
8.4	<u>Study Records</u>	22
8.5	<u>Access to Source</u>	23
8.6	<u>Retention of Records</u>	23
8.7	<u>Data and Safety Monitoring Plan</u>	23
9	<u>Study Considerations</u>	24
9.1	<u>Institutional Review Board (IRB) Review</u>	24
9.2	<u>Research Personnel Training</u>	24
9.3	<u>Study Monitoring</u>	25
9.4	<u>Unanticipated Problems and Protocol Deviations</u>	25
9.5	<u>Study Discontinuation</u>	26
9.6	<u>Study Completion</u>	26
9.7	<u>Conflict of Interest Management Plan</u>	27
9.8	<u>Funding Source</u>	27
9.9	<u>Publication Plan</u>	27
10	<u>Appendices</u>	28

1. Background

1.1 Background:

Sleep and other daily rhythm (DR) irregularities are robust risk factors for suicide thoughts and behaviors (STBs). Targeting them may have direct effects in reducing STBs, and indirect effects via multiple paths, as regularizing DRs has beneficial effects on psychiatric and other medical conditions that also increase suicide risk. Self-strategies to improve DR regularity in adolescence/young adulthood, when brain systems that DRs affect are maturing, lifelong habits are established, and STBs often first emerge, could reduce short-term, and potentially lifelong, suicide risk. While studies show negative effects of DR disruptions, research is scarce on interventions to improve DR regularity and thereby STBs and their underlying brain mechanisms. Multi-modal clinically relevant symptom/behavioral and functional magnetic resonance imaging (fMRI) measures can elucidate underlying biological and psychological mechanisms.

The Principal Investigator (PI) and Co-Investigators have long performed and have established STB research, safety methods and other infrastructure. BE-SMART-DR has shown high acceptability and feasibility, especially as most sessions are provided via secure videoteleconferencing. This suggests its potential for widespread national dissemination, broad clinical implementation, and substantial impact on the goal to reduce national suicide rates. Elucidation of brain circuitry changes could increase understanding of mechanisms underlying development and prevention of STBs, improving early risk detection and generation of additional targeted preventive strategies. Therefore, we will study BE-SMART-DR to target a hypothalamus-amygdala-ventral prefrontal cortex (vPFC) (HAV) brain system, that subserves brain functions important in STBs, e.g., emotional and other behavioral control, and is sensitive to DR changes, and anticipate that it will lead to reductions in mood symptoms and suicide propensity.

References: (please see references 1-22 in Appendices Section 10)

1.2 Prior Experience:

For the proposed study, we draw on our review of 2 decades of STB imaging studies, findings from our many years of study of adolescents/young adults with BD and MDD and in association with STBs, and methods from our international “HOPES” consortium to study brain markers of STBs, for which we are a lead site. This study was designed based on our prior NIMH-funded work with BE-SMART and our preliminary data.

2. Rationale/Significance

2.1 Rationale and Study Significance:

The purpose of this study is to advance a non-pharmacologic suicide preventive intervention with wide dissemination potential as an innovative high-yield solution to reduce suicide rates. We plan to study adolescents and young adults as they have high and rising rates of suicide, and adolescents/young adults with BD and MDD, as these disorders are present in the majority who die by suicide. There is no standard of care for this population to reduce suicide risk. We plan to study BE-SMART-DR, a modification of Social Rhythm Therapy (SRT) that provides self-directed strategies to regularize sleep and other DRs to reduce short-term suicide risk and that has shown preliminary evidence for reducing mood symptoms and suicide propensity (Sankar et al. Telehealth social rhythm therapy to reduce mood symptoms and suicide propensity in adolescents and young adults with bipolar disorder. *American Journal of Psychotherapy*, 2021 Jul 23. doi: 10.1176/appi.psychotherapy.20210011.)

2.2 Risks:

Diagnostic Assessment and Symptom Ratings: Discussing symptoms or past experiences can sometimes be stressful. These procedures will be described to the subject, and if applicable, to the legal authorized representative (LAR). Interviews will be conducted by trained staff of the Yale Mood Disorders Research Program (MDRP). Interviewers will be specifically trained to collect only information necessary for the purposes of this study. Interviews will be conducted in a professional and skillful manner. If a subject asks that information from the diagnostic interview be communicated to their community clinician and provides consent, an investigator from the study will provide the requested information to their clinician. Procedures for symptom worsening are as below.

Conditions: BE-SMART is designed to help individuals to develop healthier ways to regulate emotions, and the CC is designed to provide education about health. The therapy and CC are therefore not anticipated to worsen symptoms. They are adjunctive to outside treatments such as pharmacotherapy (i.e., no subject will be asked to modify their treatment in the community). It is possible the subject could feel worse during the course of the study. By the nature of mood disorders, symptoms of the disorders can fluctuate. If there is worsening of symptoms of concern to the subject or observed by the PI, other study personnel or their LAR if applicable, the subject can stop at any time and their study coordinator or therapist can help the subject inform their outside clinician.

Magnetic Resonance Imaging (MRI): MRI is a technique that uses magnetic and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. The subject will be watched closely throughout the study. Some people may feel uncomfortable or anxious. If this happens, subjects may ask to stop the study at any time and we will take them out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but the subject is asked to tell the research staff if they have any of these symptoms. There are some risks with an MR study for certain people. If the subject has a pacemaker or some metal objects inside of their body, they may not be in this study because the strong magnets in the MR scanner might harm them. Another risk is the possibility of metal objects being pulled into the magnet and hitting the subject. To reduce this risk, subjects are carefully

screened by trained personnel verbally and are required to sign an MRI safety sheet confirming what, if any, metal is in or on their body. We require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study when at the MRRC to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once the subject is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. Subjects are removed from the scanner immediately if they are anxious or want to stop and then are evaluated by a study clinician. Pregnant women are excluded. The neuroradiologist will review incidental findings with the PI who will provide clinical recommendations if indicated. Subjects will participate in a total of three MRI scans on their in-person visits excluding the 6-month follow-up.

EMA and Actigraphy Devices:

We will provide an actigraphy device to subjects during their participation. These devices do not have internet capability and do not hold protected health information (PHI). If a device is lost or stolen, there is no way to link the stored data to its user. The actigraphy device may be uncomfortable on the wrist of the wearer. If this happens the subject can discontinue wearing the device and return it to the study staff.

EMA questions will be similar to those used in our HIC protocol 0407026910 from the NIMH Electronic Diary Codebook (uploaded to IRES IRB Documents). The MetricWire app will prompt subjects to answer EMA questions on their smartphones. MetricWire app (developed and owned by MetricWire Inc), has previously been utilized in clinical and academic research, and is HIPPA compliant. The app encrypts data on participants' phones and while data is wirelessly transferred. The app randomly generates an identification code that contains numbers and letters and remains consistent for each subject throughout the smartphone assessment period. We will assist subjects in installing the app on their smartphone once they start their participation in the study and assist them in removing the app at participation completion. If a subject does not own a smartphone, one will be supplied for their use during their participation in this study.

Included in the EMA daily events to be rated, subjects will be asked at each assessment to what extent they are having positive and negative thoughts since last questionnaire, and to rate the impact the event had on them on a 7-point Likert scale ranging from extremely positive (1) to extremely negative (7). This impact variable will be recoded into 3 categories that indicate positive events (score 1-3), neutral events (score 4), or negative events (score 5-7).

If 'YES' is endorsed for thoughts of harming yourself or of suicide, we plan to use methods adopted by the Motor Activity Research Consortium for Health (mMarch) international mood network research consortium, led by NIMH intramural investigator Dr. Merikangas, as in their NIMH Electronic Diary Codebook Questions adapted for Adolescent Depression, as well as in our work in HIC protocol 0407026910. Subjects will receive the following alert on their device that will provide specific instructions and phone numbers to contact (as agreed in the permission/consent/ assent process).

"IMPORTANT:

The information you are providing now is **not** immediately transmitted to our study team. If you think that you are at the slightest risk of hurting yourself, please call your outside clinician and to get help right away, go to the nearest hospital or call 211 or 911. You can also call the suicide and crisis lifeline to speak with a trained counselor at: 9-8-8

Suicidal Ideation and Behavior: Only subjects who are undergoing current mental health care in the community will be enrolled in the study and outside clinicians will be communicated with for any concerns. In the event a subject is judged to be at increased risk for suicide at any time during the study, we will implement the Suicide Assessment Five-step Evaluation and Triage (SAFE-T) plan, a commonly used/validated protocol for suicide assessment. The five-step plan involves identifying risk factors and protective factors, conducting a suicide inquiry, determining risk level and interventions, and documenting a

treatment plan. For imminent risk, EMS system/Police (911) will be activated. Until EMS/police arrive, study personnel will attempt to stay with the subject if being seen in person or will attempt to stay on videotelecommunication or telephone with the subject during remote procedures that may include prescreening, the consenting process, weekly sessions, or interviews. Every subject is asked to confirm their secure and private location with study personnel at the start of any remote activities. Subjects will be removed from the study if the judgment of PI is concern of subject having active suicidal or homicidal ideation or plan.

Risk of Injury: Subjects do not give up their legal rights by participating in this study. We will not provide financial compensation for injury or lost wages for the treatment of research-related injury. The subjects (or if minors their LARs) or their insurance company will be responsible for the charges for the treatment of any physical injuries sustained as consequence of their participation in this research. Per federal regulations we will inform subjects that no financial compensation will be provided in the event of a physical injury that they sustain.

2.3 Anticipated Benefits:

There are general benefits of this research with regard to understanding the pathophysiology involved in BD and MDD and in suicide risk. Subjects assigned to the BE-SMART-DR condition may benefit by participating in the treatment by having a reduction in current symptoms and suicide risk and potentially learning beneficial lifelong behavioral strategies. Subjects assigned to the CC group may benefit from the psychoeducation provided.

3. Study Purpose and Objectives

3.1 Purpose:

The purpose of this protocol is to advance a non-pharmacologic suicide preventive intervention with wide dissemination potential as an innovative high-yield solution to reduce suicide rates and provide self-directed strategies to regularize sleep and other DRs to reduce short-term suicide risk that can be used lifelong to potentially also reduce long-term suicide risk.

3.2 Hypotheses:

Hypothesis 1: BE-SMART-DR, vs. CC, will show greater

Hyp1a: decreases in SI/P (SSI²³, CHRT²⁴) and

Hyp1b: increases in DR regularity and quality (SRM²⁵⁻²⁹, BSRS^{29,30}, PSQI³¹), and

Hyp1c: DR increases will be negatively associated with SI/P.

Hypothesis 2: BE- SMART-DR, vs. CC, will show greater

Hyp2a: hypothalamus and PFC increases, and amygdala reductions, in responses, and HAV connectivity improvements.

Hyp2b: Brain changes will be associated with DR and SI/P changes.

3.3 Objectives:

Primary Objective 1: Show pre-post BE-SMART-DR SI/P decreases associated with DR regularity and quality increases

Primary Objective 2: Show pre-post BE-SMART-DR improvements in HAV system function

Exploratory Objective: Explore, at lower and higher time intervals, indicators of BE-SMART-DR related SI/P early and sustained changes. This will include exploring if at midpoint, improved HAV function shows evidence of mediating associations between DR and SI/P changes, whether actigraphy and EMA may be earlier indicators of SI/P decreases, and if DR and SI/P improvements will be sustained at 6-months.

4. Study Design

BE-SMART-DR is a manualized 12 week intervention with weekly one-to-one sessions and between-session assignments. It is adjunctive to treatment in the community. It is a modification of the SRT part of IPSRT (Interpersonal and Social Rhythm Therapy) which is a widely used, evidenced based treatment for mood disorders (IPSRT.org). The modifications include sessions delivered by telehealth (3 sessions in person and the remainder offered by videotelecommunication) and taking into account developmental considerations (e.g., include school in addition to work, ask questions about social media). These were performed with our ongoing collaborator at the University of Pittsburgh, Dr. Holly Swartz, who is one of the founders and leading researchers of IPSRT. Our program has more than 4 years of experience in administering BE-SMART-DR. This has been in our HIC approved protocol #26910 with funding by a multi-year NIMH grant and two foundations. This protocol is similar to protocol #26910 but the funders required a separate protocol for the work of this grant. A central feature of BE-SMART-DR sessions is training participants in strategies to enhance healthy behaviors of self-monitoring and regularization of DRs. In brief, Session 1: Therapist builds rapport, discusses illness and suicide thoughts and behavior) STB history and safety planning, introduces SRT principles to connect changes in DRs to illness episode and STB onsets and the SRM (social rhythm metric questionnaire). S2: Focuses on psychoeducation about mood disorders, STBs and routines. S3-5: Devoted to understanding determinants of a stable body clock. Goals are created to achieve more regular DRs, including developing strategies that are conducive to good sleep, regular daily activities, and understanding the impact of changes in routine on mood and STBs. S6: Focuses on identification of short- and long-term DR-related goals. S7: This midpoint session reviews concepts from prior sessions, progress to date, and identifies DR-related goals for remaining sessions. S8: Devoted to understanding social media and online activity and impact on DRs. S9: Ways to anticipate/manage DR disruptions and help subjects to understand the implications of having a mood disorder, STBs and impact on their self-concept and long-term life goals. S10: Discuss impact of relationships on DRs and plans for termination. S11/12, discuss termination and have focus on warning signs, relapse presentation and safety planning around STB. S12: Final session also reviews treatment gains and clear follow-up plans. In all sessions, STBs are screened before starting and STB discussion is woven in and safety prioritized. This includes the SAFE-T plan, a commonly used and validated protocol for suicide risk assessment, based on APA guidelines.

Participants will be randomized 2:1 (provided by statistician) to BE-SMART-DR or the control condition (CC); participants will be blind to their assigned condition. The CC is modeled on previous adjunctive psychoeducational CCs widely used in randomized clinical trials of psychotherapy for mood and related disorders in adults and youths and that yield high ratings of credibility and expectancy. CC will consist of structured sessions of psychoeducational videos, monitored by a research coordinator and matched for BE-SMART-DR session number and time. CC is presented to individuals as providing a broad range of information and from which individuals can extract the most relevant portions. As with BE-SMART-DR, CC will be adjunctive to treatment as usual and include SAFE-T and other safety procedures. CC will emphasize strategies to manage the stress of a mental disorder and stigma, and health and wellness. It will offer tips on well-established self-help strategies e.g. a healthy diet, regular moderate exercise and seeking social support when distressed. As typical in similar CCs, subjects will not be provided with specific information on particular therapeutic strategies for mood disorders or STBs.

Both conditions consist of four in person visits that will take place on weeks 1, 7 and 12 and again 6 months after the subject participated in the 12th session of their assigned condition. In person visits will consist of a 90 minute MRI scanning session (3 total scans during participation) on the 3T Prisma system at the Anlyan Center and the option for the interview to be done in person or remotely. Subjects will also complete weekly self-ratings of symptoms, participate in wearing an

actigraphy device on their wrist and complete EMA when prompted using the MetricWire app on their smartphone for two week periods at the beginning, middle and end of the study.

At 6 months, after their last session, subjects will again be asked to wear actigraphy devices and complete EMA for 2 weeks prior to the 6-month follow-up interview (devices will be mailed to the subjects as needed).

In Summary:

Pre, mid, post: session, interview, self-assessments, MRI scan, 2 weeks actigraphy and smartphone EMA

Weekly over 12 weeks: sessions and self-ratings

6 months after the last session: interview, self-assessments, 2 weeks actigraphy and smartphone EMA

4.1 Study Duration:

The expected duration of subject participation is 9 months.

The estimated duration for the entire study is a minimum of 3 years.

4.2 Outcome Variables/Endpoints:

4.2.1 Primary Outcome Variables:

SI/P:

SSI: is an interviewer-administered scale that is one of the most widely used measures to assess suicidal ideation. It has 19 items scored 0–2; scoring ≥ 3 showed increased suicide risk. Its use as a primary STB measure is consistent with randomized clinical trial recommendations.

CHRT: The CHRT is a brief self-report measure that has excellent internal consistency and face validity and is used in risk assessment and to guide treatment interventions. Scores have significantly predicted suicidality-related SAEs within 6 months, controlling for mood and comorbidity, and are sensitive to changes. We will use the CHRT Propensity score (9 items) that covers domains of pessimism, helplessness, despair and perceived lack of social support. The four domains are strongly inter-correlated ($p < .001$), and each of the four domains is also strongly-correlated with the Propensity and CHRT total scores ($p < .001$). The CHRT predicts suicide attempts and events with at least 80% sensitivity in adolescents at high-risk for suicide, with a one point increase in the Propensity score associated with a 7.2% increase in the likelihood of any suicidal event and a 12.8% increase in the likelihood of a SA.

DRs:

SRM: The 5-item self-report SRM-5, with daily logs reviewed weekly, has long been used as a therapy tool. It is considered gold standard for measuring rhythm regularity with good validity and test-retest reliability.

BSRS: The BSRS is a self-rated and is a validated scale to measure DR regularity for 10 activities that include social contexts. Higher scores indicate higher irregularity. Cronbach's alpha/test-retest reliability is $82/r=.70$).

PSQI: The PSQI is a clinician administered instrument used to measure the quality and patterns of sleep. Higher scores indicate worse sleep quality; its measure “daytime dysfunctions” predicts wish to die. Sensitivity/specificity are 89.6%/86.5% for disordered sleep. Validity is supported by concurrent sleep polysomnographs.

FMRI: We will use state-of-the-art fMRI measures of hypothalamus and PFC responses, and HAV connectivity.

4.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable):

Data based on actigraphy and EMA measures will be explored. Actigraphy measures to be explored may include inter-daily stability, intra-daily variability and relative amplitude, day-time activity (M10

activity) and sleep quality (L5 activity). For EMA, we plan to explore responses to questions that include ones related to STBs, sleep and other DRs and mood.

5. Study Participants

5.1 Study Population:

We plan to enroll individuals ages 16-29 years, of all genders, sexual orientations, races, and ethnicities, in proportions representative of the population in the greater New Haven area with DSM5 diagnoses of BD I, II or OS or MDD.

5.2 Number of Participants:

We plan to enroll 128 subjects and estimate 25% attrition with 96 who complete the study.

5.3 Eligibility Criteria:

Eligibility:

Eligibility will be determined by the staff consenting subjects, who are supervised by the PI. All study personnel working with this adolescent/adult population will have completed Good Clinical Practice trainings and be IRB approved personnel.

Inclusion Criteria:

All Subjects:

1. ages 16 to 29 years
2. with DSM5 BD I, II or OS or MDD
3. will have a history of 1 or more SAs and/or a score of at least 3 on the SSI.

Exclusion criteria:

- 1) Significant medical or neurologic illness (especially if related to cerebral tissue),
- 2) MRI contraindication,
- 3) pregnancy (urine test)
- 4) current moderate or severe alcohol/other substance use disorders except caffeine/nicotine
- 5) positive urine screen for benzodiazepines, cocaine, amphetamines, phencyclidine, opiates, oxycodone; not cannabis as its use is common in this population and it can remain positive for a month
- 6) current evidence-based individual psychotherapy (e.g. cognitive behavioral therapy, dialectical behavioral therapy,) or treatment directly targeting brain regions of interest e.g. transcranial magnetic stimulation or electro-convulsive therapy,
- 7) current psychosis
- 8) inability to provide informed consent, including IQ<70, YMRS³² >25, or too symptomatic by PI's judgment
- 9) active suicidal plan or intent or Columbia Suicide Severity Rating Scale (C-SSRS)^{33,34} stage "4" risk (some intent to carry out the plan; as indicated by multisite study assessing suicide risk in RCTs or if revealed on any rating scale or in judgment of any study clinician.
- 10) homicidal ideation

5.4 Recruitment Procedures:

Through a variety of efforts, subjects will be informed about our study. Study inclusion and exclusion criteria and procedures will be discussed with Yale-affiliated clinicians, psychiatric facilities in CT including YNHPH and Silver Hill, as well as clinicians in the surrounding community. We will provide verbal and written information about the study to inform them so they may provide the verbal/written materials to interested individuals. HIC-approved advertisements for this study will be distributed widely. This includes websites (e.g. YCCI website, and the Yale University Department of Psychiatry website) and flyers distributed throughout the community (e.g., within school systems given prior authorized permission to do so) and placed at varied locations throughout New Haven and surrounding towns.

We will also be sending out information packets to area clinicians in private practice, group practices, community agencies, and public-school systems (e.g., school counselors with prior permission). In addition, the study will be discussed and contact information for the program will be provided at educational presentations. We will get HIC prior approval for flyers and ads we wish to place in media such as newspaper and magazines.

5.5 Consent/Assent Procedures/HIPAA Authorization:

Consenting will be performed in person in a private room or if remote, the subject will notify staff of their secure and private location and secure telecommunication will be used via Yale Zoom account. The HIC approved consenting study staff will read aloud and review with the subject (and LAR if the subject is a minor) the consent/assent/permission, in terms suited to the subject's comprehension, including the purposes, procedures, and potential risks associated with their participation in the study and of their rights as research subjects. Study staff will encourage questions and ensure understanding by asking open ended question about the consent information throughout the consenting process. Consenting study staff include: Hilary Blumberg MD, , program manager Susan Quatrano, study coordinators and therapists Erin Carrubba LPC and Bernadette Lecza LPC.

Both written LAR permission and adolescent assent will be obtained for all minors under the age of 18 years invited to participate. This enhances independent decision-making by never assuming the subject automatically wants to participate after reading the consent form. We will provide more time for the processing of the information when going over the assent form with the minor. We will have subjects who turn 18 years of age, during their participation in the study, sign an adult consent form at the start of their next study visit.

Signed documentation of informed consent or adolescent assent/LAR permission is required prior to starting any study procedures. The signed original forms are kept in locked cabinets in the MDRP's office suite at 60 Temple Street. Subjects signing remotely will be asked to send the signed form or a photo of the signed form to study staff via mail, email, or fax.

Subjects/LARs have the option to decline participation, or if they have initially agreed to participate to withdraw their/ the minor's participation at any time during the study. They can talk with the minor's outside clinician about other treatment options or find an alternate study to participate in. They will be informed that withdrawing from the study will involve no penalty or loss of benefits to which they are otherwise entitled and will not harm their relationship with their own doctors or with Yale-New Haven Hospital. Subjects will be reimbursed for any parts of the study they have participated in and travel expenses as indicated in the HIC-approved consent/permission/assent forms.

Compound Authorization and Consent/Assent/Permission Forms (attached in IRES):

1. For Subjects with a Mood Disorder: Psychotherapy Study for Ages 18 Years and Older
2. For Subjects with a Mood Disorder: Psychotherapy Study for Ages 13-17 Years
3. For Legally Authorized Representative of an Adolescent with a Mood Disorder: Psychotherapy Study for Ages 13-17 years

Consent to Video/Audio Recordings are attached to each of the 3 forms above

6. Study Methods/Procedures

6.1 Study Procedures:

Pre-screening will be performed by study staff by phone, video telecommunication or in-person. Collected information will be limited to the necessary PHI for re-contact and to determine eligibility.

The privacy of the potential participant and the confidentiality of information collected about them will be protected by utilizing the same procedures as done in the screening visit.

At the screening visit, a member of the research team will discuss all aspects of the study: its purpose, the procedures that will be performed and potential risks of the procedures. If the potential subject is considered eligible for the study and agrees (and the LAR if the subject is a minor) to enroll, the potential adult subject or minor/LAR will be asked to sign the consent or assent/permission form(s). Once consented, the subject will participate in research interviewing, self-assessments, MRI scanning, a session, receive the actigraphy device, will be assisted in downloading the EMA MetricWire app on their smartphone or provided a smartphone with MetricWire app for use for the following two weeks. This visit will last approximately 7-8 hours.

The subject/LAR will sign a Release of Information form that will allow us to contact the subject's outside clinician and provide them with the information on their patient's participation and to provide contact information for study staff in the event concerns arise. The release may also be helpful in clarifying information such as diagnosis and, if necessary, requesting psychiatric medical records for review for diagnostic and treatment history information.

Study personnel will administer an interview to the subject and, if minor, the LAR will additionally be interviewed about the subject in private and separately from the subject to ensure privacy. The interview may be performed in person in a private office or remotely in a private secure telecommunication room (Yale Zoom account). Remote subjects will notify staff of their secure and private location before the interview starts.

Prior to scanning, subjects will be asked to practice computerized versions of the tasks that will be administered in the scanner to familiarize them with the functional MRI. We will also collect urine to test for toxicology and, if the subject is female, test for pregnancy. Results of the testing will be discussed only with the subject, including if the subject is a minor. A member of the research team will accompany the subject to the Anlyan Center and remain for the duration of the scanning that takes approximately 90 minutes. The scanning will be performed on a 3-Tesla Prisma MR scanner.

The conditions consist of either 12 weeks of a weekly manualized one-to-one therapy session lasting under 1 hour and between-session assignments or 12 weeks of a weekly viewing session of pre-taped videos lasting under 1 hour and overseen by a study coordinator. First, mid and last sessions (weeks 1, 7, 12) will be in-person at the MDRP; remaining sessions will be offered remote by secure video or audio telecommunication, as subjects reported this enhanced convenience, adherence and this yielded high ratings of credibility and expectancy. The CC will consist of structured sessions, matched for BE-SMART-DR session number and time. The week 12 session for CC participants will be conducted in-person as a 1:1 session with the study coordinator. As with BE-SMART-DR, CC will be adjunctive to treatment as usual and include SAFE-T and other safety procedures. CC will offer tips on well-established self-help strategies to manage health and wellness e.g., a healthy diet, regular moderate exercise and seeking social support when distressed. As typical in similar CCs, strategies will not be provided for the regularization of DRs that are considered the active ingredients of BE-SMART-DR.

Visit Schedule (with economic compensation consideration):

Weeks 1, 7, 12: In person visits will include: Session (remote option available), interviewer ratings (remote option available) (\$30), self-ratings (\$10), MRI (\$50), EMA (\$15), actigraphy (\$15). Additionally, week 1 cognitive testing (\$30) will be included. Total week 1: \$150; weeks 7 and 12: \$120.

Weeks 2-6, 8-11: Remote session and self-ratings (\$10): Total for 9 remote visits: \$90.

6-month follow-up: Interview and self-ratings (\$30), EMA (\$15), actigraphy (\$15):

Total: \$60

Overall total for the visits: \$540.00

Subjects will be compensated/reimbursed cash at the end of each in person study visit (this will include compensation for remote sessions and self-ratings since last in person visit). For subjects completing between-visit components and unable to attend their visit in-person, they will be compensated with a digital gift card emailed to them by their study coordinator.

Subjects will be reimbursed for reasonable travel expenses and if parking at Temple Street or Temple Medical garage the subject will be reimbursed \$22. Any other reasonable expenses will be made per PI discretion.

The research procedures and use of devices are free of charge, but we do ask that any devices provided for use during the study are returned back to staff after each use.

Self-Ratings Completed by Subjects

Completed Daily:

-* SRM (BE-SMART-DR subjects complete daily for duration of participation).

Completed Weekly and at 6-Month Follow-Up:

-*Altman Self Rating Mania Scale (ASRM)*^{35,36}: a scale designed to assess the presence and/or severity of manic symptoms (5 items)

-*Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)*³⁷⁻³⁹: a scale to screen for depression and measure changes in severity of symptoms (16-items)

*The following information will be provided in Qualtrics prior to filling out the first question of this inventory as one question refers to suicidal ideation. The information provides specific instructions and phone numbers to contact (as agreed in the permission/consent/ assent process).

“IMPORTANT:

The information you are providing now is **not** immediately transmitted to our study team. If you think that you are at the slightest risk of hurting yourself, please call your outside clinician and to get help right away, go to the nearest hospital or call 988, 211, or 911. You can also call a suicide hotline to speak with a trained counselor at:

1-800-273-TALK (1-800-273-8255)

or

1-800-SUICIDE (1-800-784-2433).

Completed at Week 1 only:

-*Edinburgh Handedness Inventory (EHI)*^{40,41}: a questionnaire that assesses right- and left-hand preference with good test re-test reliability (10 items)

-*Childhood Trauma Questionnaire (CTQ)*^{42,43}: a scale that measures 5 types of maltreatment that are associated with increased risk for suicide (28 items)

-Pubertal Development Scale (PDS)⁴⁴: a questionnaire that rates pubertal development ranging from immature to fully developed

-Gender Identity and Sexual Orientation⁴⁵: a self-rated questionnaire on gender identity and sexual orientation (3 items)

-COVID-19 Exposure Rating: We've chosen relevant COVID-19 exposure questions for a self-rating that were taken from longitudinal surveys that allow for data sets to be comparable. The questions in the COVID-19 Rating were selected from the following sources:

- Welcome longitudinal population studies (LPS) (website pending)
- COVID-Mental Health tracker (COVID-MH) (<http://www.suicideresearch.info/tracking-the-impact-of-the-covid-19-pandemic-on-mental-wellbeing-study-covid-mh>)
- UCL COVID-19 Social Study (UCLSS) (<https://www.covidsocialstudy.org/>)
- The Coronavirus Health Impact Survey (CRISIS) (<http://www.crisissurvey.org/>)

Completed Weeks 1, 7, 12 (and 6-Month Follow-Up excluding SRM):

-SRM, BSRS, PSQI and CHRT

-Actigraphy wearable over a 2 week period.

-EMA via MetricWire app on smartphone 4x/day over a 2 week period

-Barratt Impulsiveness Scale-11 (BIS-11)⁴⁷: a scale that measures trait impulsiveness which is associated with risk for suicide behavior (30 items)

-Beck Hopelessness Scale (BHI)⁴⁸: a scale designed to assess the extent of positive and negative beliefs about the future. Hopelessness will be assessed as it is a leading risk factor for suicide (20 true/false items)

-Difficulties in Emotion Regulation Scale (DERS)^{50,51}: a measure used to assess the emotion regulation problems among adolescents and adults (36 items) -Emotion Reactivity Scale (ERS)⁵²: a measure of emotion sensitivity, intensity, and persistence (21 items)

-Munich Chronotype Questionnaire (MCQT)⁵³: a scale to assess individual phase of entrainment on work and work-free days (19 items)

-NIH PROMIS Medication Adherence Scale (PMAS)⁵⁴: a scale used to assess self-reported medication adherence behaviors (12 items)

Completed Week 12 only:

-Client Satisfaction Questionnaire (CSQ)^{55,56}: will assess satisfaction with treatment (8 items)

Assessments Administered by Study Staff

Collected at Visit 1 only:

-Socioeconomic Status (SES)⁵⁷: a widely used assessment of socioeconomic status

-The Wechsler Abbreviated Scale of Intelligence (WASI)⁵⁸: a widely used brief interviewer administered IQ test designed to assess specific and overall cognitive capabilities

-Family History – Epidemiology (FHE)⁵⁹: an assessment used to collect pedigree psychiatric information (after week 1, if any indication there could be a change, will repeat)

-Pittsburgh Structured Clinical Interview for Sleep Disorders (SCID-SLP)⁶⁷: an instrument provided by our collaborator used to identify history of sleep issues (after week 1, if any indication there could be a change, will repeat) (after week 1, if any indication of sleep issues, will repeat)

-Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD)⁶⁶: a semi structured diagnostic interview to assess the 10 DSM-5 Personality Disorders as well as Other Specified Personality

Collected at Weeks 1, 7, 12 and 6-Month Follow-Up:

-Child and Adolescent Services Assessment (CASA)⁴⁹: a reliable self- and parent-report instrument, used to track mental health services

-Columbia Suicide History Form (CSHF)^{33,34}: considered a gold-standard scale to gather history of lifetime suicide behavior (after week 1 only interim changes will be assessed)

- Columbia Suicide Severity Rating Scale (C-SSRS)*^{33,34}: is a questionnaire widely used in clinical and research settings to assess the severity of recent suicidal ideation and behavior (after week 1 only interim changes will be assessed)
- Hamilton Depression Rating Scale (HDRS)*^{62,63}: a widely used rating scale used to assess symptoms of depression; the 29 item version probes “atypical” depressive symptoms often present in mood disorders in adolescents and young adults (29 items)
- Medical Lethality Suicide Scale (MLS)*⁶⁴: an interviewer-administered scale that measures the medical severity of suicide attempts
- Scale for Suicide Ideation (SSI)*²³: a widely used rating scale that assesses current intensity of attitudes, plans, and behaviors to commit suicide (19 item)
- Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version (K-SADS-PL)*⁶⁵ (for minors only): a semi-structured diagnostic interview that provides assessment of present episode and lifetime history of psychiatric illness in children according to DSM-IV criteria. It has good test-retest and inter-rater reliability. The K-SADS-PL is completed by interviewing the child and his/her LAR separately. Final diagnoses are made by incorporating all sources of data and using best estimate procedures. It will be used to confirm psychiatric diagnosis and items may be explored in analyses (after week 1, interview for changes)
- Structured Clinical Interview for DSM SCID-5 for Adults Aged 18 and Over – Present and Lifetime Research Version (SCID-5)*⁶⁶: a structured diagnostic interview that provides assessment of present episode and lifetime history of psychiatric illness in adults according to DSM-5 criteria. It is completed by interviewing the subject. It will be used to confirm psychiatric diagnosis and items may be explored in analyses (after week 1, interview for changes)
- Young Mania Rating Scale (YMRS)*³²: a clinician administered tool used to rate the severity of symptoms of mania (11 items)

Collected weeks 1, 7, 12:

- MRI Metal Screening Form (filled out by participant/LAR and reviewed with staff)
- MRI Data Form (includes height and weight from which will calculate BMI, current medications, menstrual phase)
- Urine for toxicology and for females pregnancy

6.1.1 Data Collection:

The data are collected, recorded and stored by trained research personnel. The subject may be asked to utilize a computer or phone for sessions via videotelecommunication, wear an actigraphy device, use a smartphone to respond to EMA prompts and fill out self-reports through Qualtrics. Subjects will complete self ratings through the Yale approved online software survey, Qualtrics. Clinical ratings and assessments (paper/pencil) administered by study staff will contain no PHI and be stored in locked file cabinets in a locked office suite. Data will be recorded onto master excel spreadsheets that will be saved on a Yale secure server. Scanning data is collected by trained technologists and will be stored on password-protected and encrypted computers in compliance with HIPAA regulations.

There is no identifiable data on the actigraphy device we supply and they do not have GPS or any other location recording capability. Deidentified raw actigraphy activity data is downloaded to a desktop app and converted to files that only the researchers on this project can match to subjects. EMA responses submitted using MetricWire app are immediately synced to HIPAA-Compliant servers in the United States and removed from the subject’s smartphone. The data are encrypted end-to-end during transmission and MetricWire servers use an Encryption Token to verify that the data is coming from the correct source (authenticity) and that the data have not been modified in-transit (integrity).

Video and audio recordings through ZOOM will be hosted by Yale staff with Yale Zoom accounts, which are HIPAA compliant.

Letter and number codes with the link to subjects' identifiers will be stored in a separate computer file on the Yale University fileserver and access will be limited to authorized personnel. This file will be backed-up in encrypted form using Yale University encryption software and will be stored in encrypted form on office desktop computers located in the locked office suite at MDRP. Only de-identified subject data will also be stored on unencrypted electronic databases. Laptops and computers will be password protected.

6.2 Method of Assignment/Randomization (if applicable):

Subjects will be blind and randomized 2:1 using block randomization to BE-SMART-DR or CC. Subjects will be blinded to assignment. The therapist will not be blinded, but the staff member administering the structured interviews at weeks 1, 7, 12 and 6 months will be blinded to subjects' condition.

6.3 Adverse Events Definition and Reporting:

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

6.4 Reaction Management:

Study personnel will be trained in safety, risk and protection methods.

All subjects participating in this study will have an outside clinician and this clinician will be communicated with by study staff should any concerns arise. If a study clinician believes it will be beneficial to the subject or the subject/LAR requests, we will speak with their clinician.

The SAFE-T plan will be discussed with the subject at initial visit and referred to and implemented throughout the study as needed.

For imminent risk, EMS system/Police (911) will be activated. Study personnel will attempt to stay on videotelecommunication or with participants until EMS/Police arrive. Subjects will be removed from the study if the judgment of the PI is concern of the subject having active suicidal or homicidal ideation or plan.

Subjects will be prompted to complete daily EMA questions and depending on how they respond may receive the following information:

If you think that you are at the slightest risk of hurting yourself, please call your outside clinician and to get help right away, go to the nearest hospital or call 211 or 911. You can also call a suicide hotline to speak with a trained counselor at:

1-800-273-TALK (1-800-273-8255)

or

1-800-SUICIDE (1-800-784-2433).

6.5 Withdrawal Procedures:

Subjects are free to stop and withdraw from this study at any time during its course. Information on withdrawal procedures is provided in the informed consent forms and will be discussed with the

subject during the consenting process. Subjects may also ask that their data be anonymized and can take away permission to use and disclose of their health information at any time. Subjects may withdraw their permission by telling the study staff or by writing to the PI, Dr. Hilary Blumberg, at MDRP 60 Temple ST Suite 6B, New Haven, CT 06510. This will cancel any future appointments.

Withdrawing from the study will involve no penalty or loss of benefits to the subjects and will not harm their relationship with their doctors or with Yale-New Haven Hospital. When a subject withdraws from the study, no new identifying health information will be gathered after that date. Information that has already been gathered may still be used and given to others as necessary to ensure the integrity of the study and/or study oversight.

The researchers may withdraw subjects in the research if necessary. This may occur, for example, if the researchers believe the subject may need more services than there are provided in this protocol or if new exclusion criteria emerge.

6.6 Locations/Facilities:

Mood Disorders Research Program, 60 Temple St. Suite 6B and Magnetic Resonance Research Center at the Anlyan Center, 300 Cedar Street

7. Statistical Design

7.1 Sample Size Considerations:

Hyp 1a,b Power: Estimating 25% attrition, power is based on 64 BE-SMART-DR and 32 CC completers and assume an $\alpha=.05$ threshold for primary analyses. We estimate that we will have 80% power to detect small/medium within-subject difference for both BE-SMART-DR ($d'=0.36$) and CC ($d'=0.51$) groups. For between-group comparisons, we can detect a medium effect of $d\geq 0.61$.

Hyp 1c Power: We estimate that our proposed sample will provide 80% power to detect small/medium associations both across ($r=.28$) and within (BE-SMART-DR $r=.34$, CC $r=.47$) groups.

Hyp2a/b/c Power: We estimate that our proposed sample will provide 80% power to detect small/medium associations both across ($r=.28$) and within (BE-SMART-DR $r=.34$, CC $r=.47$) groups.

These estimates compare favorably with anticipated effects and estimates in our pilot data.

7.2 Planned Analyses:

Statistical consultation will be available with Dr. Blumberg's longstanding collaborators Ralitz Gueorguieva and Brian Pittman, experts in analyses of clinical and neuroimaging data. Prior to hypothesis testing, descriptive statistics and graphs will be used to summarize the data. Distributions of summary scores will be examined for outliers. Data will be checked for adherence to normal distribution using normal probability plots and Kolmogorov-Smirnov test. If necessary, transformations will be used to meet assumptions for analyses. If this cannot be achieved, appropriate nonparametric methods will be used.

Hyp1a/b Testing: Linear mixed models will evaluate rating scales (Hyp1a: SSI, CHRT; Hyp1b: SRM, BSRS, PSQI) as dependent variables with time (pre-, post-session) as a within-subjects factor and group (BE-SMART-DR, CC) as a between-subjects factor. All interactions will be modeled. Least square means and standard errors will be estimated and plotted to assess significant effects. Exploratory analyses will assess sensitivity of results after adjustment for community-based mental health treatment, and medication classes, doses, adherence, duration by including the variables as additional predictors in the models. Additional covariates e.g. demographic, symptom, behavior, course and other illness features, as above will be considered in the models, one at a time.

Hyp1c Testing: Pre-post change scores for DRs (SRM, BSRS, PSQI) and SI/P (SSI, CHRT) will be calculated. An ANCOVA model will include SI/P changes as dependent variables, and group and DR changes as between-subjects factors. Overall and group slopes will be estimated from the model.

Hyp2a/b/c Testing: HAV system changes (Hyp2a) will be analyzed using a similar mixed model as described for Aim1a above, with region (hypothalamus, amygdala, vPFC) included as the within-subjects factor. Associations between brain changes and symptom/behavioral (DR, SI/P) changes (Hyp2b) will be analyzed as for Hyp1c.

7.2.1 Secondary Objective Analyses:

To test whether early changes in the HAV system mediate BE-SMART-DR effects on SI/P, early (pre-mid) DR changes (SRM, BSRS, PSQI) will serve as predictor, and early brain changes as mediators, while pre-post changes in SSI, CHRT will represent the dependent variables. A series of regression models testing for between-group differences in the mediator and the outcome, and testing for associations between the mediator and outcome, will be employed. A last regression model will test the joint effects of both group and the mediator. We will examine model coefficients to determine any partial or full mediating effects of brain function on BE-SMART-DR-induced reductions on SI/P. The estimated indirect effect will be tested for significance using bootstrapping procedures. Changes in Actigraphy/EMA measures will be analyzed using a similar model as described for Hyp1a/b. Secondary analyses will examine more refined changes over time using all available time points, including binned EMA/actigraphy summary measures (see below). We will fit time as categorical since we do not a priori know whether the change over time will be best described with a linear or curvilinear function. In post hoc analyses, we will test for linear and quadratic effects of time or will consider transformations of time (e.g. log) to assess which shape best describes the patterns of change in repeated measures over time. Sustained SI/P and DR changes will be modeled similarly to Hyp1a/b.

7.3 Data Relevance:

The data will be collected to accomplish the study aims and test the study hypotheses.

7.4 Data Coding:

Data will receive an alpha numeric code that does not have identifiers. The link between the code and identifiers will be stored on Yale's secure server and access will be only by the PI and selected program personnel, such as program manager Susan Quatrano.

7.5 Data Analysis Tools:

Imaging software to be used will include widely used and locally developed programs such as BioImage Suite (www.bioimagesuite.org) software. Analyses will also be performed using widely used software, such as SAS (Cary, NC).

7.6 Data Monitoring:

See Study Monitoring Section 9.3

7.7 Handling of Missing Data:

All analyses will be intent-to-treat and will be based on mixed models for regions of interest. The mixed effects approach is advantageous as it is unaffected by randomly missing data and allows greater flexibility in modeling the correlation structure of repeated measures data. Sensitivity analyses under informative dropout will be performed as necessary.

8. Data/Specimen Handling and Record Keeping

8.1 Subject Data Confidentiality:

Subject confidentiality and privacy is strictly held by the participating investigators, their staff, and the sponsor(s)/funding agency. All staff members that come into contact with the data are fully trained to the current HIPAA regulations and are informed as to the proper use of all data.

Representatives of the Institutional Review Board (IRB), regulatory agencies or funding agency may inspect all documents and records required to be maintained by the investigator for the subjects in this study. The study site will permit access to such records.

The collection of sensitive PHI will be limited to only what is necessary to achieve the aims of the research; only trained study personnel will collect this data. All research activities will be conducted in as private a setting as possible. The subject will be asked to do sessions in a location where the subject can speak confidentially. There is no identifiable data on the actigraphy or EMA devices that we supply, and they don't have GPS or any other location recording capability. If a device is lost, there is no way to track it back to the user as it doesn't hold personally identifying information. Deidentified raw actigraphy and EMA data is downloaded to a desktop app and converted to files that only the researchers on this project can match to subjects. Hard copy documents with PHI will be kept in a locked cabinet within a locked office suite and other data without PHI will be kept separate from PHI. Subject research data will be identified by a unique alphanumeric code that does not have any identifying information and will be stored separately from the subject's contact or identifying information.

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor/funding agency requirements.

8.2 Data Quality Assurance:

Quality control and assurance of data will be a continuous practice and will happen in real-time, close enough to the data collection to ensure the integrity and validity of the data. Errors will be corrected as soon as possible following identification. Unexpected errors requiring new corrective procedures will be addressed with PI as soon as possible.

The subjects themselves directly enter their self-reported data into Qualtrics as they respond to survey items. Staff complete a review of the data entered for each subject following the completion of each visit. Data entered into a master spreadsheet will be cross checked for errors by another member of our staff. Scanning data will be analyzed quarterly with quality control analyses to confirm scanner functionality and that the task is functioning correctly.

8.3 Data or Specimen Storage/Security:

See 6.1.1 Data Collection

8.4 Study Records:

The PI will ensure that staff with delegated responsibilities for generating, recording, reviewing, and maintaining clinical data and records follow the most stringent requirements and comply with IRB/HIC and institutional requirements, policies and procedures. This may include (but are not limited to) regulatory documents, protocols, consent forms, medical records, laboratory reports, subject diaries, subject questionnaires and recorded data.

8.5 Access to Source:

The PI will ensure study staff maintains adequate and accurate source documents and records that include all pertinent observations on each subject. Source data will be attributable, legible, contemporaneous, original, accurate, and complete. When making changes or corrections, the original entry will be crossed out with a single line, initialed and dated, will be traceable, will not obscure the original entry, and will be explained if necessary. All study staff will protect confidentiality of records that could identify subjects in accordance with all applicable regulatory requirements.

Upon request of the monitor, auditor, IRB/HIC, or regulatory authority, the investigator will make all requested clinical related records available for direct access in order to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

8.6 Retention of Records:

Once all data for this project has been collected and results of these studies published, study data will remain securely stored at MDRP indefinitely after being stripped of all subject identifiers by zeroing and will be available to other qualified researchers. Any such request for study data which meets reasonable standards of scientific integrity will be considered.

When the study is over, the MetricWire Research Team will delete EMA data collected for this study from their servers and they will not retain any additional copies of the data on their servers or in the MetricWire application.

8.7 Data and Safety Monitoring Plan:

This protocol presents greater than minimal risks to the subjects and AE are not anticipated, but the potential exists for anticipated and/or unanticipated AEs, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. In the unlikely event that AEs occur, serious unanticipated AEs will be reported within 48 hours to the HIC (using HIC form 6A) and within 10 business days to the National Institutes of Health. The investigator will specify whether the serious unanticipated AE is considered related to the study.

We will summarize all adverse and unexpected events in our annual request for re-approval application to the HIC. The PI will evaluate the adverse and unexpected events and study data at one-year intervals and determine whether the adverse and unexpected events affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to subjects) or consent form (at Risks and Inconveniences) are required. The PI will be responsible for overall data and safety monitoring of this protocol.

The risks associated with the current study are deemed for the following reasons:

1. We do not view the risks associated with BES-MART-DR as minimal risks.
2. Given the now established safety and validity of the current BE-SMART-DR in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated AEs, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Attribution of Adverse Events:

AEs will be monitored for each subject participating in the study and attributed to the study procedures / design by the PI (Hilary Blumberg, MD) according with the following categories:

- a.) Definite: AE is clearly related to investigational procedures(s)/agent(s).
- b.) Probable: AE is likely related to investigational procedures(s)/agent(s).
- c.) Possible: AE may be related to investigational procedures(s)/agent(s).
- d.) Unlikely: AE is likely not to be related to the investigational procedures(s)/agent(s).
- e.) Unrelated: AE is clearly not related to investigational procedures(s)/agent(s).

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of AEs noted during the study:

- 1. Mild AE
- 2. Moderate AE
- 3. Severe

Plan for Determining Seriousness of Adverse Events:**Serious Adverse Events:**

In addition to grading the AE, the PI will determine whether the AE meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if:

- 1. Death;
- 2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
- 3. A persistent or significant disability or incapacity;
- 4. A congenital anomaly or birth defect; OR
- 5. Any other AE that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An AE may be graded as severe but still not meet the criteria for a SAE. Similarly, an AE may be graded as moderate but still meet the criteria for an SAE. The PI will consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

9. Study Considerations**9.1 Institutional Review Board (IRB) Review:**

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required. Study closure will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

9.2 Research Personnel Training:

All study personnel working with this child/adolescent/adult population will have completed Good Clinical Practice trainings and Human Subject Protection Training (HSPT).

Study personnel include experts in clinical care, and research assessments and studies of adults and children with mood disorders and with suicide thoughts and behaviors. Research staff members have been specifically trained in the administration of the assessments of the proposed study and have established high reliability. Study staff not providing subject therapy or sessions will be blinded to condition and will administer diagnostic, symptom and behavioral/cognitive testing to BE-SMART-DR and CC subjects on weeks 1, 7, 12 and at 6- month follow-up.

The 2 therapists (also performing research coordinator functions at MDRP) are trained in assessments related to emotion processing and regulation, mood and suicide in children and adults

and each have >20yrs experience administering research therapies and by study start >4 years in BE-SMART-DR. They will be randomly assigned to cases across conditions with emphasis placed on ensuring they understand the important distinctions of each and there is no “bleeding” between BE-SMART-DR and CC, in order to preserve data integrity/fidelity. Drs. Blumberg, Silverman will closely supervise each therapist weekly. To be eligible to rate, raters will score within one point of each other on each scale item. All sessions will be recorded and 25% of sessions, randomly selected, will be rated for fidelity. Of these, 10% will be rated by both raters to ensure inter-rater reliability.

9.3 Study Monitoring:

The PI will provide ongoing supervision and evaluation of the activities of the study, including the frequency and severity of adverse events and whether new risks have been identified and whether appropriate progress is being made. Personnel responsible for the safety review and its frequency:

The PI will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the PI (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The PI, the Institutional Review Board (IRB) or the HIC or the study sponsor have the authority to stop or suspend the study or require modifications.

We will have an Independent Safety Monitor (ISM) who will be an independent physician and appropriate expert with relevant expertise whose primary responsibility will be to provide independent study monitoring.

9.4 Unanticipated Problems and Protocol Deviations:

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions have been developed by the site and will be implemented promptly.

The PI is responsible to identify and report Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) including adverse events that meet the reporting criteria and therefore should be considered as UPIRSOs. UPIRSOs may be medical or non-medical in nature and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the prompt reporting requirements described in IRB Policy 710 will be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. All deviations will be addressed in study source documents.

The PI will report the following types of adverse events to all Co-Investigators on the protocol, study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Any incident, experience or outcome that meets ALL 3 of the following criteria:

Unanticipated problems involving risks to subjects or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Timeframe for Reporting:

1. Events that may require a temporary or permanent interruption of study activities by the PI or sponsor to avoid potential harm to subjects will be reported to the IRB immediately (if possible), followed by a written report to the IRB using the UPIRSO Reporting Form (710 FR 4) no more than 5 calendar days after the Yale PI becomes aware of the event.

2. Internal Events will be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) within 5 calendar days of the PI becoming aware of the event.

3. External Events should be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) within 5 calendar days of the Yale University PI becoming aware of the event ONLY IF either of the following are true:

(a) The Yale PI has concluded that an immediate change to the protocol is necessary to address the risks raised by the event, OR

(b) A monitoring entity (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) has required modifications/amendments to the research protocol or consent documents as a result of the event.

The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

9.5 Study Discontinuation:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.6 Study Completion:

The expected date of study completion will be at least 3 years after the official start date. A study closure form will be submitted for IRB to review and verify the study is eligible for closure. If longer time is needed to complete the study, extensions will be requested to the HIC.

9.7 Conflict of Interest Management Plan:

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All investigators will follow the applicable conflict of interest policies.

9.8 Funding Source

American Foundation for Suicide Prevention

9.9 Publication Plan

The PI has primary responsibility for publishing the study results and the sponsor does not have requirements for their involvement in publication.

10. Appendices

Appendix #	Title	Section	Topic
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